Neurology

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JULY--1959

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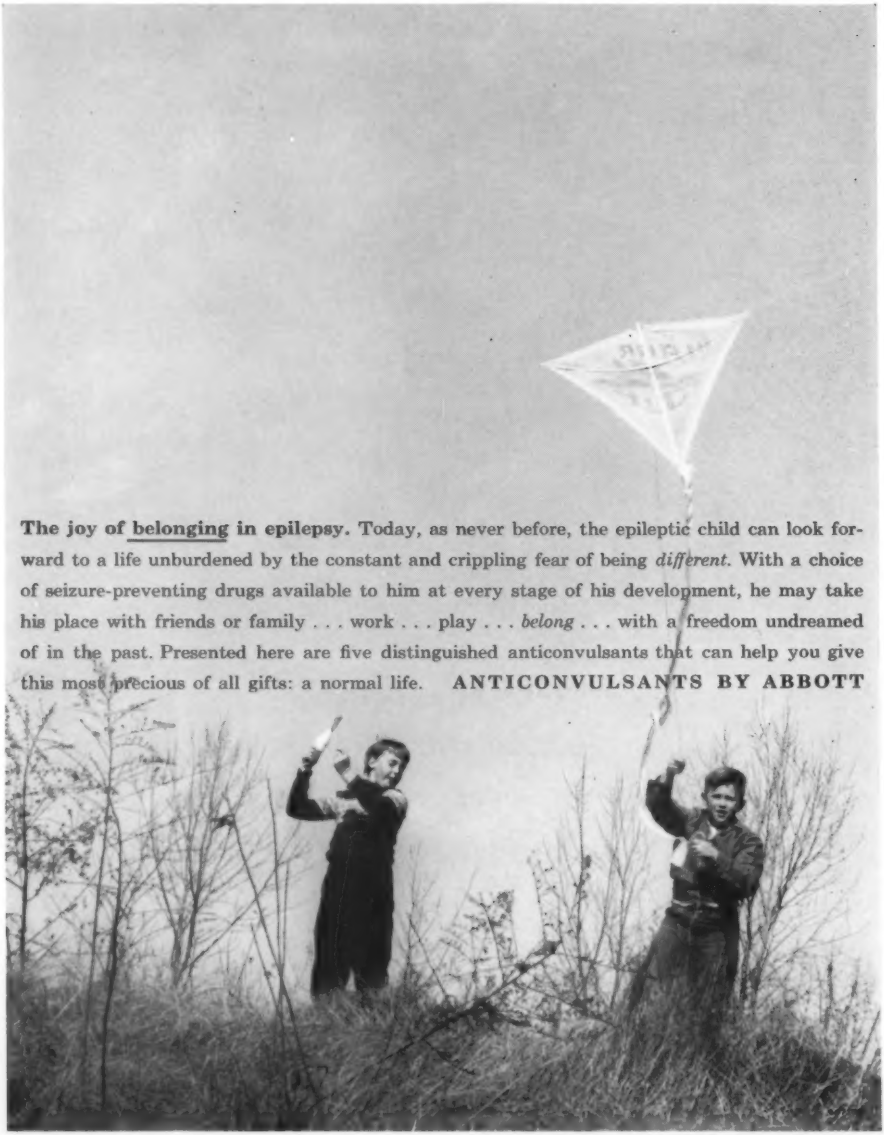

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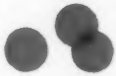

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Manuscripts of papers read at meetings of the Academy must be filed with the secretary at the time of the meeting, and will be published if acceptable to the editorial board. They are the property of the Academy, and authors who wish to publish them elsewhere must first request release.

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"The most striking aspect of thioridazine [Mellaril] therapy is the poverty of side effects.... In its lack of side effects and low toxicity, it is superior to all other tranquilizing drugs tested. For this reason also it is well tolerated by patients, particularly those who are not hospitalized and who frequently discontinue their medication because of dizziness, sleepiness, increased tension or parkinsonism with other drugs."[2]

NEGLIGIBLE SIDE EFFECTS

"Side effects were negligible at all dosage levels: no incidence of parkinsonism or other extrapyramidal symptoms. Minimal sedation, on the whole lower than with other tranquilizing agents. No alteration in liver function, urine or blood. No photosensitivity. Patient acceptability was exceptional: lack of drowsiness, lethargy or 'washed out' feeling, permitted patients to carry on normal everyday activities. Orthostatic hypotension was absent. The initial 'keyed up' tense feeling common to other drugs of this type was absent.... Patients forced to interrupt treatment with other phenothiazine derivatives because of parkinsonism or other extrapyramidal symptoms were able to continue therapy with thioridazine without appearance of parkinsonism."[2]

SINGULARLY FREE OF SIDE EFFECTS

"The extrapyramidal syndrome was not encountered in any of its forms. Dizziness and sleepiness responded to a reduction in dosage. Other side effects did not occur.... It is singularly free from the side effects ordinarily seen with these [phenothiazine] compounds."[4]

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"None of the following toxic effects, so common after administration of the phenothiazines, was present during the period of Thioridazine administration: Parkinsonism or Parkinson-like symptoms, photosensitivity, orthostatic hypotension, bone-marrow depression."[1]

MINIMAL SIDE EFFECTS

"Side effects such as extrapyramidal activity, jaundice and photosensitivity have not been observed in patients treated with Thioridazine [Mellaril]. Extrapyramidal side effects produced by other phenothiazines have disappeared promptly with no deterioration in the behavioral response when these patients have been shifted to Thioridazine."[5]

NO JAUNDICE

"No allergic reactions were observed such as skin eruptions, jaundice or agranulocytosis. Central nervous system toxicity, as manifested by extrapyramidal effects, seizures, and excitement did not occur despite the use of high doses (up to 2000 mg.) of the drug."[6]

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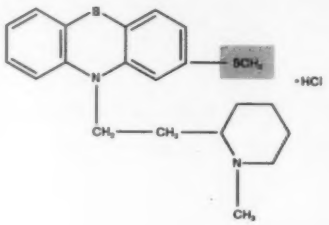

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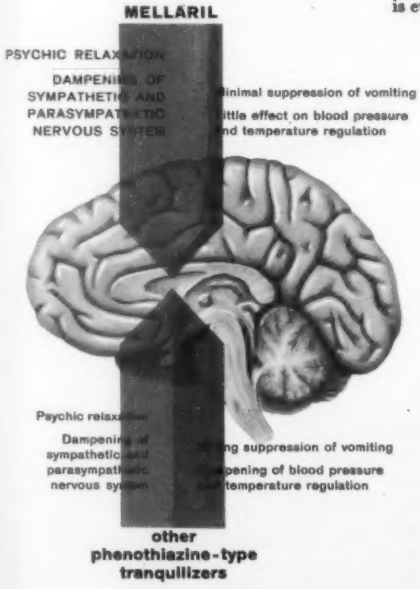

2 **Less "spill-over" action to other brain areas — hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.**

3 **A notable absence of extrapyramidal stimulation.**

4 **Lack of impairment of patient's normal drive and energy, while achieving psychomotor control in mental and emotional disorders.**

5 **Virtual freedom from toxic effects — jaundice, photosensitivity, skin eruptions, disturbed body temperature regulation, blood forming disorders have been absent in reports currently available.**

These properties add up to a greater margin of safety in general office practice, in ambulatory psychiatric out-patient clinics, and in hospitalized patients.

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excellent clinical response

In office practice and in hospitalized patients, Mellaril has proved highly useful for a wide variety of major and minor emotional disorders (such as anxiety, tension, apprehension, alcoholism, agitated psychoneurosis, agitated psychotic states, etc.).

EXTREMELY SATISFACTORY "... produced extremely satisfactory results in the broad therapeutic range represented in this series."[3]

POTENT AGENT "... appears to be a potent agent in the symptomatic management of a variety of psychiatric states."[4]

MAJOR ADDITION TO THERAPEUTICS "This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."[1]

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"...extremely satisfactory results..."
in a clinical spectrum ranging from
minor nervous disorders to
severe psychotic disturbances[3]

RESULTS WITH MELLARIL IN 194 PATIENTS[3]

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83% satisfactory effect	68% satisfactory effect	57% satisfactory effect
Some cases had complete remission of symptoms. Most were able to return home to useful occupations.	Relief of symptoms in cases permitted easier management and a return to a more or less useful life.	Some cases, complete relief of symptoms. Other cases, partial relief of symptoms.

RESULTS WITH MELLARIL IN PATIENTS PREVIOUSLY TREATED WITH OTHER TRANQUILIZERS[3]

DIAGNOSTIC CATEGORY	IMPROVED %	VERY SATISFACTORY %	SATISFACTORY %	UNSATISFACTORY %
SCHIZOPHRENIA				
Acute	89	61	28	11
Chronic paranoid	84.2	31.6	52.6	15.8
Chronic, other	73.9	21.7	52.2	26.1
Residual	57.1	9.5	47.6	42.9
CHRONIC BRAIN SYNDROME	66.6	33.3	33.3	33.3
CHRONIC PSYCHONEUROSIS	62.5	12.5	50	37.5
CHRONIC PSYCHOSOMATIC DISORDERS	75	25	50	25

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a guide to administration and dosage

Dosage ranges from 10 mg. three or four times a day in milder situations to 25 mg. three or four times a day for more disturbed patients. In ambulatory psychiatric out-patients, dosages of 50 to 100 mg. three or four times a day have been found adequate. For severely disturbed hospitalized psychotics, dosages of 200 to 300 mg. three times a day may be administered.

Dosage must be individualized according to the condition and degree of response. In all cases, the smallest effective dosage should be determined for each patient.

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
	ADULTS	
Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneurosis, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
	CHILDREN	
BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

PRECAUTIONS: Although possessing a unique structure and a selectivity of action which broadens its therapeutic ratio, the physician should be alert to the possibility of untoward reactions in certain susceptible individuals. In particular, he should watch for potential hemopoiet depression, jaundice or orthostatic hypotension. As wi other phenothiazines, Mellaril is contraindicated i severely depressed or comatose states from any cause.

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- controls neurotic and psychotic patients with anxiety, apprehension, nervous tension
- virtual absence of jaundice, parkinsonism, photosensitivity, dermatitis
- minimal sedation and drowsiness
- does not mask organic conditions such as brain tumors, intestinal obstruction, etc., because of lack of anti-emetic action
- increased specificity of action results in greater safety at all dosage levels

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References: **1.** Doshay, L. J.; Constable, K., and Zier, A.: Neurology **3**:360, 1953. **2.** A.M.A. Council on Drugs: New and Nonofficial Drugs, Philadelphia, J. B. Lippincott, p. 242, 1958. **3.** Brock, S., Mod.: Bull. New York Acad. Med. **32**:202, 1956. **4.** Doshay, L. J.: Parkinsonism and Its Treatment, Philadelphia, J. B. Lippincott, pp. 87-88, 1954. **5.** Doshay, L. J.: J.A.M.A. **162**:1031, 1956.

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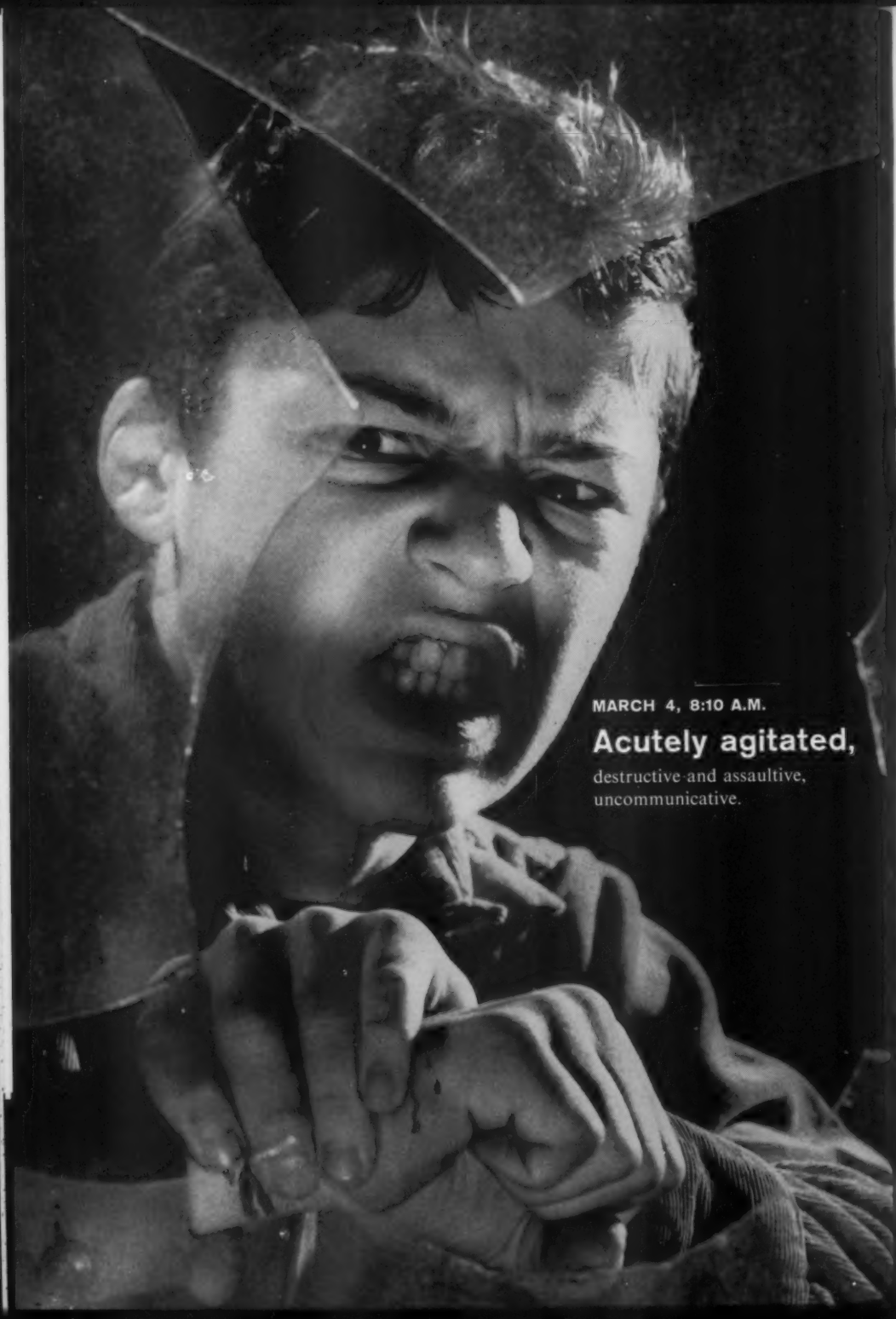
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Acutely agitated,
destructive and assaultive,
uncommunicative.

RCH 4, 10:00 A.M.
RINE, I.V., has been given.
ient in light sleep.
n be awakened readily,
l responds to questioning.

MARCH 5, 2:00 P.M.
Receiving oral SPARINE.
Quiet but alert. Contrite
about smashed window.

MARCH 8, 9:00 A.M.
Still on oral
SPARINE, maintenance
dosage. Ready
for psychotherapy.

RINE quickly controls acute psychotic episodes, then maintains trol while definitive psychiatric treatment is provided. SPARINE ilitates accessibility, speeds rehabilitation, simplifies care.

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first report on a new and significant antidepressant

the new, rapidly effective treatment for true (endogenous) depressions, affective or organic

Nardil™

brand of phenelzine dihydrogen sulfate

restores the depressed, despondent or suicidal patient to reality without recourse to E.C.T.[1-4]

QUICK-READING SUMMARY

chemistry-pharmacology: Nardil, first discovered in 1956 by Scott and Chessin,[5] is beta-phenylethylhydrazine dihydrogen sulfate, a powerful inhibitor of monoamine oxidase in the brain.[6]

clinical response: many depressed patients respond with an elevation of affect within 4 to 8 hours. Self-deprecatory feelings and even suicidal ideation rapidly subside. Depression is lifted without the over-stimulation of sympathomimetic amines. Recovery generally occurs within 2-6 weeks. E.C.T. was not required.

side effects, toxicity: clinical trials since 1957 have revealed no toxic effects on blood, liver or kidneys. Few side effects have been encountered. However, dosage levels higher than recommended may produce transient postural hypotension, constipation, impotence or delayed micturition.

WARNER CHILCOTT

NORRIS PLAINS, N.J.

first report on a new and significant antidepressant

Nardil™

brand of phenelzine dihydrogen sulfate

a brain-specific monoamine oxidase inhibitor

the new, rapidly effective treatment for true (endogenous) depressions, affective or organic

restorative activity apparent in hours

•

objective antidepressant response in days

•

complete recovery in 2 to 6 weeks

•

side effects transient and mild

Common among the experience reported by several investigators during the Nardil trials was this new drug's speed of action, high percentage of complete to good remissions, the absolute lack of toxicity and the infrequency and mildness of side effects.

Many patients report a lift in mood within four to eight hours. A new sense of purpose is accompanied by a rapid dispersal of self-deprecatory feelings, ruminative thinking and suicidal ideation. Sleep and appetite are improved.[1]

Sainz[2] reported that, of his series of 122 patients, 89 per cent of the depressed affectives and 82 per cent of other endogenous depressions had complete remissions following Nardil.

Maximum improvement was always noticed not later than five weeks after the onset of therapy.[2] This investigator then concluded that Nardil "...appears to be the treatment which most clearly compares to electrocoma therapy in scope, rapidity of action and freedom from serious side effects."[2]

This observation has also been made by Thal[1] as a result of his experience with Nardil in 180 patients with true (endogenous) depressions. "In the treatment of depression, the response to this antidepressant therapy approaches the response generally obtained from electro-shock therapy. Eighty per cent of patients were discharged from the hospital as recovered within 60 to 90 days following commencement of treatment with Nardil." Electroconvulsive therapy was not used in any case.

Saunders and colleagues[3] found that all their patients with true (endogenous) depressions recovered within 10 to 15 days of therapy with Nardil.

In over 1,000 patients to date: *liver dysfunction did not occur, clinical hypotension was rare.*

Nardil has a preferential distribution to the brain—not the liver. The investigations of Sainz[2] in 122

COMPARATIVE EFFECTIVENESS*

General diagnosis	Patients	ECT % Satisfactory Response	Iproniazid % Satisfactory Response	Patients	Nardil % Satisfactory Response
endogenous depression, overt	11	72	45	26	78
endogenous depression, larval	3	—	100	12	86
affective psychosis, depressed phase	8	87	42	19	89

*Adapted from Sainz, A.

moderate to markedly depressed patients revealed that Nardil was "...less toxic than iproniazid because no hepatic, hemopoietic or central nervous system parenchymatous damage (had) occurred or been foreshadowed." The experience of Thal[1] in 180 patients, and that of Saunders[3] as well, disclosed no toxic effect after careful analysis of liver function tests and blood studies.

Postural hypotension has appeared among a few patients given Nardil in a dosage range higher than that recommended.[2] But since the incidence does not appear to be clinically significant, it does not detract from Nardil's particular value in ambulatory as well as hospitalized patients.

Indications: Nardil is indicated in the treatment of true (endogenous) depressions of an affectual or organic nature. Depression associated with catatonic schizophrenia may be relieved, although Nardil itself has no effect on schizophrenic mechanisms.

Side Effects: The occasional side effects which have been reported include postural hypotension with the expected associated signs, transient impotence, nausea, ankle edema, delayed micturition and constipation. These can be adequately managed by appropriate adjunctive therapy or will abate as dosage is reduced to the maintenance level.

Caution: Even though no toxic effects on the liver have been reported with the use of Nardil, as a matter of caution patients should be carefully followed with liver profile studies and the drug should be withheld or used with extreme care where the patient has a history of liver disease or where liver damage is present. Also, hypotensive patients should be under close medical supervision.

Dosage: Recommended starting dose is one 15 mg. tablet three times a day with meals. Improvement is usually seen within one week. After maximum benefit is achieved, usually over a period of several weeks, the dosage is slowly reduced to a maintenance level depending upon individual needs and may be as low as 15 mg. daily. In the occasional patient who does not respond to the above starting dose, an additional one or two 15 mg. tablets may be given at bedtime.

Supply: Bottles of 100 orange-coated tablets, each containing 15 mg. phenylethylhydrazine present as the dihydrogen sulfate.

References: 1. Thal, N.: Cumulative Index of Antidepressant Medications. Dis. Nerv. System 20:197 (May) 1959. 2. Sainz, A.: The Phrenopraxic Activity of a Non-noxious Antidepressant, Ann. New York Acad. Sc. (in press) 1959. 3. Saunders, J. C.; Roukema, R. W.; Kline, N. S., and Bailey, S. d'A.: Clinical Results with Phenelzine, Am. J. Psychiat. (in press) 1959. 4. Report of Clinical Trials with Nardil in 800 Patients. Warner-Chilcott Department of Clinical Investigation, 1959. 5. Chessin, M.; Dubnick, B.; Dramer, E. R., and Scott, C. C.: Modifications of Pharmacology of Reserpine and Serotonin by Iproniazid, *Fed. Proc. 15*:409, 1956. 6. Chessin, M.; Dubnick, B.; Leeson, G., and Scott, C. C.: Biochemical and Pharmacological Studies of B-phenylethylhydrazine and Selected Related Compounds, Ann. New York Acad. Sc. (in press) 1959.

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Literature supplying details on dosage and administration available on request.

*Carter, S.: *M. Clin. North America:* 315 (March) 1953.

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Neurology Volume 9 • Number 7

Cerebrovascular Disease:

III. The intracerebral arterioles

A. B. Baker, M.D., and A. Iannone, M.D.

ARTERIOLES ARE CONSIDERED to be muscular arteries of reduced size. No sharp line divides the arterioles and the muscular arteries. Most investigators now use vessel size in preference to designating the vessel type.

Kernohan, Anderson, and Keith[1] limited the size of the arterioles to vessels of 25 to 100 μ in fixed tissue. Maximow and Bloom[2] designated vessels of as large as 300 μ as arterioles. In the present study, we have placed the upper limit of the arteriole diameter at 150 μ.

The literature on the normal structure and alterations in these vessels is very inadequate. In 1884, Obersteiner[3] described the normal changes in these small arteries in 91 cases. The vessels were characterized by their well-formed internal elastic lamina, the absence of elastic fibers in the media, and the paucity of adventitia. In the smaller arterioles, the internal elastic lamina was very delicate and disappeared as the caliber of the arteriole diminished. The muscle media was relatively thick and composed of spindle-shaped muscle fibers which encircled the blood vessel. Obersteiner described a connective tissue degeneration of these vessels which proceeded from the middle coat and ultimately replaced the entire vessel, resulting in the formation of a fibrous cord. Such changes were seen in perfectly healthy brains, even in children, but were much more frequent in patients over 60. Even when these small vessels became completely occluded, the surrounding brain tissue showed no tissue changes.

Neuberger,[4] in his description of the degenerative changes in the cerebral arteries, reported a diffuse hyperplastic sclerosis of the cerebral arterioles. This consisted of a hyaline degeneration of the vessel wall which begins in the intima and only later implicates the media and adventitia with narrowing of the vessel lumen.

In 1935, Baker[5] studied the structure of these small cerebral arteries and their changes with age. He believed that these vessels were characterized by: [1] a relatively thick internal elastic lamina, [2] a media composed of both muscle and collagenous fibers with the latter often predominating, and [3] an adventitia of variable thickness. With the advance of age, the elastica becomes reduplicated and frequently loses its tinctorial properties. The media undergoes fibrosis as well as hyalinization.

Supported by a grant from the National Institute of Neurological Diseases and Blindness of the United States Public Health Service.

From the Division of Neurology, University of Minnesota Medical School, Minneapolis.

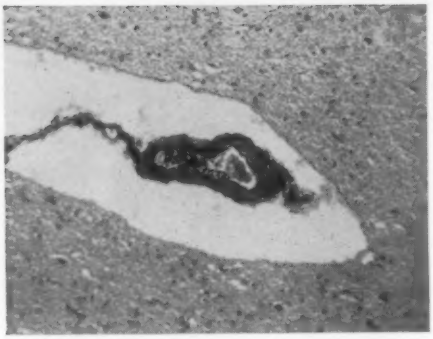

Fig. 1. Arteriole of 150 μ. in a 46-year-old subject. The elastica is seen as a fine, wavy, homogeneous membrane. (Weigert-Van Gieson stain × 200)

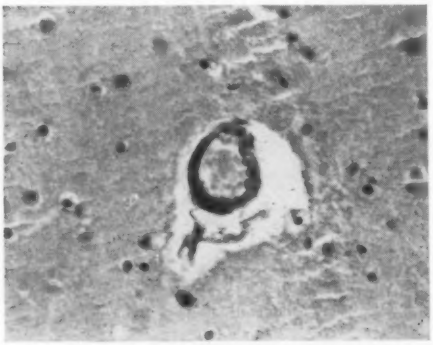

Fig. 2. Small 45 μ. arteriole in a 29-year-old patient. The vessel wall is composed of a few muscle fibers surrounding a very thin straight elastic membrane. (Weigert-Van Gieson stain × 500)

Seitelberger[6] also reported on the age changes in the smaller cerebral arteries. He found that the cells of the media disappear and that the entire vessel wall is replaced by hyaline material. Thus, in elderly patients, one finds fibrous vessels almost exclusively.

Because of the paucity of literature on this subject, the present study was undertaken and consists of a review of the structure of the arterioles in 100 consecutive subjects. Blocks were taken from representative areas throughout the brain and sections were stained with hematoxylin-eosin stain, Weigert-Van Gieson stain, and Weigert's elastic-tissue stain.

NORMAL CEREBRAL ARTERIOLES

In contrast to the arterioles elsewhere in the body where the vessel wall often is very thick, the arteriolar wall in the brain is very thin, often measuring only 15 μ in a vessel of 150 μ in diameter. The walls of these vessels may be divided into the 3 regular vascular layers—intima, media, and adventitia. Microscopic study of these vessels does not always reveal clear-cut divisions between these layers.

Intima. This inner coat is composed of an endothelial layer and an elastica interna. The endothelium is a very delicate membrane composed of a simple layer of flattened cells. This membrane is often not detected in the arterioles, and, at best, only an occasional endothelial cell can be seen. The internal elastic membrane is a compact, wavy structure that stains uniformly (Fig. 1). As the vessel decreases in size, the elastica becomes less wavy and rapidly decreases in thickness until it finally consists of a few strands of thin fibers lining the lumen of the vessel (Fig. 2).

Media. The media is the thickest of all layers and, in many of the arterioles, comprises all of the remaining vessel wall, since adventitia is usually absent. The media is composed of circularly arranged muscle fibers. The larger vessels contain a well-defined muscular layer within which many muscle nuclei can be seen. The small arteries may be composed of very few muscle fibrils, and only a few muscle nuclei can be observed (Fig. 2). Delicate collagenous strands may be present but are few in number in the average arteriole of a young individual. The basic tissue within the media consists of smooth muscle, and the collagenous fibers are usually few and inconspicuous. Elastic fibrils are also very scarce and almost never detected, even with special stains.

Adventitia. The adventitial layer is quite variable. Even in the larger arterioles, this layer is composed of only a few strands of collagenous tissue. In the smaller vessels, the adventitia completely disappears. In vessels under 70 μ, no adventitial layer can be detected and practically all of the vessel wall is composed of muscle media (Fig. 2).

DEGENERATIVE CHANGES

The degenerative changes observed in these small arteries already have been described by one of us (A. B. B.). These changes will now be reviewed and supplemented by newer observations from our present studies.

Intima. The endothelial lining generally remains unchanged. The internal elastic lamina, however, is frequently altered. Although this structure is usually a solid uniform band, the lamina begins to show areas of reduplication. At first, this consists of an irregular fraying of the solid lamina and the forming of tiny, fine fibrils which project irregularly from various portions of the main lamina. In addition to this splitting of the elastica, changes also occur in the tinctorial properties of this membrane. The elastica loses its ability to stain normally with the usual dyes and appears patchy and indistinct. Ultimately, the entire elastica fails to stain and is difficult to discern on microscopic studies.

Media. This layer bears the brunt of the degenerative changes in the arterioles. An early increase is observed in the connective tissue elements which results in radially arranged, fine and coarse collagenous fibers which seem to fuse with one another. The collagenous tissue soon comprises a large proportion of this lamina and, in many cases, makes up the greatest bulk of the wall (Fig. 3). Throughout this connective tissue are found varying amounts of obliquely arranged muscle cells and nuclei. The muscle tissue is quite irregular in occurrence and is often entirely absent from a part or from the entire vessel wall. Ultimately, the media undergoes complete fibrosis and the entire vessel is comprised of a collagenous tube lined by a thin, indefinite elastic membrane and a few endothelial cells (Fig. 4).

In some of the larger arterioles of 125 to 150 μ which possess an adventitial layer, an adventitial proliferation may result which compresses and replaces the outer medial wall, leaving a fibrous vessel that still retains a thin rim of muscle tissue adjacent to the vessel lumen. Aside from this thin rim of muscle elements, one cannot differentiate between the media and adventitia—since these 2 layers appear to have merged.

These medial degenerative changes usually do not become arrested at this point. The heavy collagenous fibers lose their outline and assume a homogenous, hyalinized appearance. This process also appears to implicate the internal elastic lamina; the entire vessel now appears as a small, homogenous, acellular structure.

At this stage, the vessel wall is not increased in thickness and the vessel lumen is not narrowed. Apparantly, all the changes have occurred within the elements already present in the arteriole and this type of degenerative

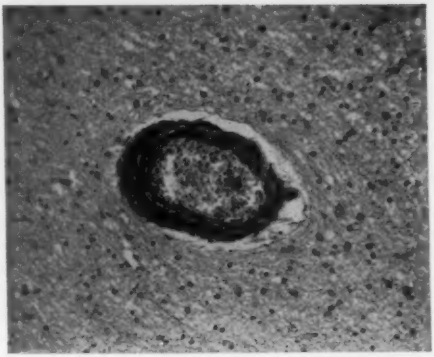

Fig. 3. Replacement of an arteriole wall by collagenous tissue. Note that the connective tissue increase is irregular, producing varying thickness of the wall. The elastica is still visible as a fairly uniform, straight membrane. (Van Gieson stain × 200)

Fig. 4. Complete fibrosis of a small intracerebral vessel of 100 μ. (Weigert-Van Gieson stain × 200)

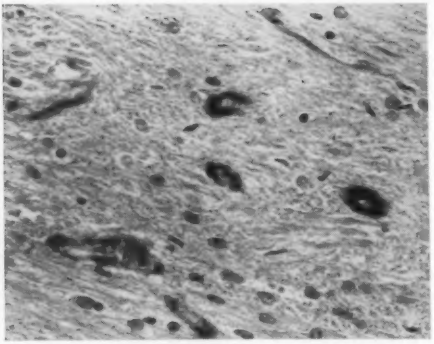

Fig. 5. Hyalinization of many arterioles with thickened walls and narrowed vessel lumens. Note that the surrounding tissue shows no alteration. (Van Gieson stain × 500)

process does not become arrested at this point. In older individuals, this hyalinization process continues to progress to a point where the vessel wall has become greatly thickened and the vessel lumen narrowed. Many of these arterioles become completely occluded by this process. However, in spite of the occlusion of many of these small vessels in a single area, the surrounding tissues reveal no changes (Fig. 5).

The final and least common type of degenerative change is calcification of the wall elements. The calcium is at first deposited as irregular, tiny particles in the outer portion of the media. The deposition may increase and replace large portions of the vessel wall. This calcification is independent of any other change within the wall and may occur with or without hyalinization or fibrosis of wall elements.

Adventitia. Most of the arterioles contain no adventitia. The larger ones that do contain adventitia show only adventitial increase with replacement of the media.

Basal vessels. The degenerative changes already described occur also in the basal vessels, only much more extensively and earlier. The medial musculature disappears very rapidly so that these vessels rapidly assume a fibrous appearance. Hyalinization and calcification of the vessel wall are quite frequent and usually well advanced by an early age.

DISCUSSION

In contrast to the other cerebral arteries, the most constant degenerative changes within the arterioles occur within the media and consist of a progressive fibrosis of the vessel wall. In our previous studies of these vessels, these changes were consistently correlated with the age of the patients. We believed that this arteriolar fibrosis was predominantly an age change. In order to verify this observation, the degree of degenerative change within the arterioles was correlated with the age of the patients (Table 1). It is apparent from this tabulation that an excellent correlation exists between age and the severity of arteriolar disease. During the first three decades of life, the arterioles are usually uninvolved. During the fourth and fifth decades, changes begin to appear and become very marked after the fifth decade. This age correlation is so consistent that one feels justified in saying that medial fibrosis of the arterioles is a normal age change.

As early as 1872, Gull and Sutton[7] described arteriolar changes in the kidneys in chronic glomerulonephritis and described these changes as arteriocapillary fibrosis. In 1925, Fishberg[8] studied the arteriolar changes in 72 patients with essential hypertension. He found arteriolar fibrosis in the kidneys of all patients, while one-fifth of brain arterioles were similarly implicated. Since then, many studies have revealed the great frequency of arteriolar changes in the brain in persistent hypertension.[9–11] The arteriolar changes described are similar to those seen and described by us as a normal age change for these vessels. The striking difference, however, is the age at which these changes occur. Normally, arteriolar fibrosis first appears during the fourth decade and becomes severe only during or after the fifth decade. In cases of persistent hypertension, severe arteriolar fibrosis can occur during the second and third decades, at ages when arteriolar fibrosis normally is not seen.

In order to recheck this observation, our cases were reviewed for instances in which arteriolar fibrosis occurred at an earlier than usual age period. Severe fibrosis occurred within the third and fourth decades of life in 6 patients. Review of these case histories revealed that 3 of these patients had a definite hypertension or heart weight of over 500 gm.,

TABLE 1
CHANGES IN ARTERIOLES WITH AGE

Age	*Normal*	*Moderate*	*Severe*
0 to 10	9 or 100%		
11 to 20	8 or 100%		
21 to 30	7 or 100%		
31 to 40	4 or 80%		1 or 20%
41 to 50	1 or 10%	7 or 70%	2 or 20%
51 to 60		18 or 78%	5 or 22%
61 to 70		5 or 50%	5 or 50%
70		10 or 36%	18 or 64%

while 2 had severe, longstanding diabetes. Only 1 patient revealed no apparent cause for this premature fibrosis.

From these observations, one can conclude that arteriolar fibrosis actually is a physiologic change occurring with age and that any condition such as hypertension or diabetes may cause a pathologic exaggeration or acceleration of this physiologic process.

Since the degenerative changes in the larger cerebral vessels did not show an accurate correlation with age, one would not expect to find any consistency in arteriolar changes when compared to changes in the larger vessels in the same patient. Nevertheless, we believed that such a tabulation might be of interest to again point out the individualization of the degenerative arterial changes both as to degree and etiology. Such a comparative study is outlined in Table 2. That severe arteriolar changes often occur in the complete absence of any degenerative changes in the larger arteries of the brain can be readily seen. It is apparent from this table that any discussion of cerebrovascular disease must take into account the vessel size and the basic type of change that occurs in these arteries.

SUMMARY

1] The normal arteriole is considered to have a maximum diameter of 150 μ.

2] These small blood vessels normally consist of a thin, homogenous, elastic membrane, a muscular media of a few layers thickness and no adventitia, except in a few of the larger arterioles.

3] The chief degenerative changes in these vessels are limited to the media and consist of a progressive medial fibrosis which ultimately replaces the entire vessel wall.

4] The vessel wall may finally become hyalinized—with a definite thickening of the vessel wall and a narrowing or complete occlusion of the lumen.

TABLE 2
ARTERIOLAR CHANGES AS COMPARED TO ALTERATIONS IN OTHER CEREBRAL ARTERIES

	Arteriolar changes		
	Normal	*Moderate*	*Severe*
Small arteries 150–500 μ.			
Normal	18 or 90%	16 or 40%	11 or 36%
Moderate	2 or 10%	13 or 33%	14 or 45%
Severe		11 or 27%	6 or 19%
Large basal arteries			
Normal	14 or 74%	19 or 48%	10 or 32%
Moderate	5 or 26%	16 or 40%	9 or 30%
Severe		5 or 12%	12 or 38%

5] Parenchymal changes do not result from complete occlusion of these small vessels.

6] This arteriolar fibrosis appears to be a normal physiologic process beginning in the fourth decade of life and increasing in severity with the age of the patient.

7] Various somatic processes, such as hypertension and diabetes, may accelerate this physiologic process so that arteriolar fibrosis may appear at an earlier stage in life.

8] The frequency and severity of the degenerative changes differ in the cerebral arteries of different size. Any study of cerebrovascular disease must, therefore, consider carefully the artery size and the type of degenerative change characteristic for this size vessel.

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Intracranial hemorrhage as a complication of anticoagulant therapy

Kevin D. Barron, M.D., and Guillermo Fergusson, M.D.

IN RECENT YEARS, anticoagulant drugs have been employed widely in the treatment of thromboembolic disorders. Of particular interest to neurologists are the current encouraging reports on the use of anticoagulants in cerebral embolism and intermittent insufficiency syndromes accompanying occlusive disease of the carotid and basilar arteries.[1–4] Inherent in anticoagulant therapy is the danger of serious or fatal hemorrhage. Established complications include genitourinary and gastrointestinal bleeding, hemoptysis, epistaxis, cutaneous ecchymosis, hemorrhage from wounds, retroperitoneal hemorrhage, and hemorrhage into serous cavities. The present report concerns intracranial hemorrhage accompanying the administration of anticoagulants. Case reports of 5 recently observed patients are given, and the literature on the subject is reviewed. It is concluded that cerebral hemorrhage is a serious hazard of anticoagulant therapy in hypertension and recent cerebral infarction.

CASE REPORTS

Case 1. A 45-year-old woman with mitral stenosis and auricular fibrillation was admitted to Montefiore Hospital on September 23, 1956. Five days previously, she had sustained a transient left hemiplegia. Examination at the time of admission disclosed an apical diastolic murmur, auricular fibrillation, slight left hemiparesis with hyperreflexia, and a blood pressure of 120/80 mm. Hg. Commissurotomy was performed on September 26, 1956. Recurrent attacks of sudden left upper quadrant abdominal pain occurred postoperatively, and a pleural friction rub developed at the left base. On October 8, 1956, the patient had an attack of left hemiparesis lasting twenty minutes. Anticoagulants were administered; by October 10, the patient had received 300 mg. of heparin and 500 mg. of Dicumarol in divided doses. At 5:30 A.M. on that date, the patient had a seizure and lapsed into coma, with deviation of the head and eyes to the right and bilateral Babinski signs. She died within eighteen hours. The prothrombin time twelve hours before death was 35.4 sec., with a control of 13.4. A clotting time of 17 min. was recorded three hours before death.

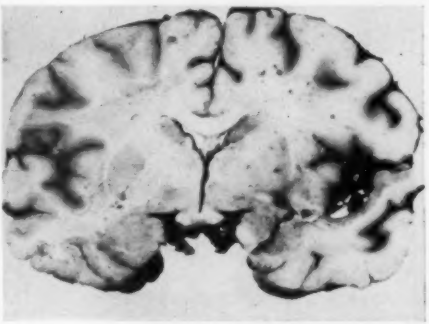

Fig. 1. (*Case 1*) Note diffuse subarachnoid hemorrhage. The right Sylvian fissure is distended by blood. The defect in the right amygdaloid nucleus is an artefact.

Pertinent extracranial postmortem findings included healed rheumatic mitral and aortic valvulitis, slight mitral and aortic stenosis, moderate hypertrophy of the right and left ventricles, organizing thrombus in the stump of the left auricular appendage, emboli to the renal arteries, and multiple splenic and renal infarcts.

Macroscopic examination of the brain revealed diffuse subarachnoid hemorrhage (Fig. 1). In the right Sylvian fissure, clotted blood attained 12 mm. in thickness and surrounded the right middle cerebral artery. Both middle cerebral arteries were occluded at their points of origin by soft, brown, friable blood clots. The major cerebral vessels were carefully dissected to their peripheral ramifications and found to be thin walled and elastic. No aneurysms, anomalies, or other occlusions were noted. Coronal sections disclosed apparent extension of the subarachnoid bleeding into the orbital cortex of the right frontal lobe for a distance of 5 mm.

From the Laboratory Division, Montefiore Hospital, New York City.

Drs. Barron and Fergusson are trainees of the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, Public Health Service, Bethesda, Md.

Fig. 2. (*Case 2*) Note massive cingulate herniation on the right. Hemorrhage extends into both frontal lobes.

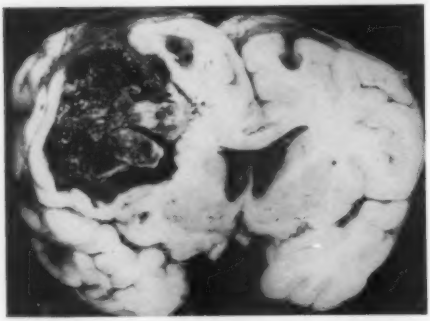

Fig. 3. (*Case 3*) The large hemorrhage into the right hemisphere has ruptured through the cortex. The ventricles contain casts of blood.

This was the only site of intracerebral hemorrhage. The left basal ganglia contained 4 zones of cystic malacia. The third and fourth ventricles contained casts of blood.

Hematoxylin-eosin and Nissl preparations of the right frontal and temporal cortex and basal ganglia showed widening of perivascular and perineuronal spaces and interstitial edema. Neurons showed ischemic cell change. Hemorrhage into the cerebral subarachnoid space appeared fresh. The bleeding into the orbital gyri was superficial and interpreted as an extension from the leptomeningeal hemorrhage. Both middle cerebral arteries were occluded by recent blood clots composed of partially lysed red blood cells, disintegrating leukocytes, and fibrin. The embolus on the right side seemed slightly older. The walls of the middle cerebral vessels were normal histologically, and intramural hemorrhage was not observed.

Case 2. A 46-year-old man was admitted to Montefiore Hospital on April 9, 1957, for treatment of congestive heart failure. Rheumatic heart disease had been diagnosed at age 13. At age 33, a right hemiplegia appeared suddenly but disappeared completely within one week. Congestive heart failure occurred at age 41, and auricular fibrillation persisted from that time. At age 44, another right hemiplegia developed; recovery again was complete. Over the years, episodes suggestive of splenic and renal infarction were numerous. Since 1955, the patient was maintained more or less continuously on Dicumarol. He always had been normotensive, and the blood pressure at the time of final admission was 120/70 mm. Hg. Mitral commissurotomy was performed on July 5, 1957. Dicumarol was discontinued before and for three days after operation. On July 14, the patient had a grand mal seizure. No neurologic sequelae ensued. At 7 P.M. on July 17, sudden onset of left hemiplegia and stupor was associated with bloody spinal fluid under increased pressure. Despite administration of vitamin K_1 and tracheostomy, the patient died twenty-four hours later. The prothrombin time shortly after onset of the final episode was 41.8 sec., with a control of 13.8.

Postmortem examination disclosed healed rheumatic mitral valvulitis with stenosis. All cardiac chambers were dilated and hypertrophied. The left auricle was particularly enlarged but did not contain thrombus.

The right hemisphere of the brain was soft and swollen. The cerebral leptomeninges were stained with blood. The right cingulate gyrus and right uncus were herniated massively (Fig. 2). Upon careful dissection of the cerebral arteries, no abnormalities were found. Coronal sections disclosed an enormous hemorrhage occupying almost the entire centrum semiovale on the right side. The right basal ganglia were obliterated, and the entire ventricular system contained a cast of blood. Anterior to the precentral gyrus, the hemorrhage had ruptured through the cortex. A smaller hemorrhage on the left side was confined to the white matter of the left frontal lobe. Numerous petechiae were found in the brain stem tegmentum.

Histologic examination of both hemispheres by the hematoxylin-eosin method revealed fresh intracerebral hemorrhages. Red blood cells were well preserved. The margins of the lesions showed no microglial or astrocytic reaction. The white matter and cortex not disrupted by hemorrhage had a pallid, edematous appearance, and neurons in the cortex overlying zones of hemorrhage were chromatolytic, or shrunken, darkly stained, and lacking in sharp detail. The pontine tegmentum was the site of numerous petechial hemorrhages centered about small, thin-walled, dilated vessels. Careful search of multiple sections of the hemispheres and brain stem did not disclose embolic material.

Case 3. A 70-year-old white woman had long standing rheumatic heart disease and medically controlled congestive heart failure. She always had been normotensive and free of neurologic symptoms. The patient was admitted to Montefiore Hospital on January 1, 1956, after sudden onset of

crampy pain in both lower limbs followed by numbness, weakness, and bluish discoloration. These symptoms were of eight hours' duration. General physical examination revealed a blood pressure of 104/70 mm. Hg; dyspnea; moist rales in both lower lobes; and cold, mottled, paralytic lower limbs, with absent femoral pulses. Therapy with Dicumarol and heparin was instituted on admission; heparin was discontinued on January 5. On January 7, the prothrombin time was 42 sec., with a control of 13.8. She was found dead in bed at 5:45 A.M. on January 8.

Extracranial postmortem findings were healed rheumatic valvulitis, with mitral stenosis and dilation and hypertrophy of the left auricle; thrombus in left auricular appendage; embolus and retrograde thrombus at the bifurcation of the aorta; gangrene of the lower limbs; and fresh infarctions of the left kidney.

Gross examination of the brain revealed diffuse subarachnoid hemorrhage (Fig. 3). In the right cerebral hemisphere, a huge, frontoparietal hemorrhage had ruptured into the ventricular system. At one point, the hemorrhage had disrupted the cerebral cortex and escaped into the subarachnoid space. The white matter of the right hemisphere unaffected by hemorrhage was swollen, and the right cingulate gyrus had herniated beneath the falx. No occlusions of the cerebral vessels were detected. The major arteries had only slight arteriosclerotic change, and neither aneurysms nor vascular anomalies were found.

Microscopic sections stained by the hematoxylin-eosin method showed massive, fresh hemorrhage. Red and white blood cells were well preserved. The white matter and cerebral cortex in the vicinity of the hemorrhage appeared edematous. Embolic material was not found in any of the microscopic preparations.

Case 4. A 60-year-old Negro woman had had dyspnea, cough, dysphagia, and speech difficulty for six months. She had been hypertensive for many years. On admission to Montefiore Hospital on January 2, 1957, examination disclosed obesity and enlargement of the heart to the left. The blood pressure was 210/110 mm. Hg. A soft-tissue density in the superior mediastinum was seen on the chest roentgenogram.

While being investigated, the patient had an episode diagnosed as pulmonary embolism. Dicumarol was administered. On the twenty-second day of treatment, the prothrombin time was 34.4 sec., with a control of 11.2. The next morning, the patient complained of headache and lapsed into coma, with flaccid right limbs and a dilated, fixed, right pupil. The blood pressure had remained at hypertensive levels and, at onset of coma, was 210/110 mm. Hg. Lumbar puncture revealed bloody spinal fluid. Death occurred at 3:00 P.M. on the twenty-third day of Dicumarol therapy. The final prothrombin time was 38.2 sec., with a control of 12.

Postmortem findings, exclusive of the nervous system, were generalized arteriosclerosis, left ventricular hypertrophy, innominate artery aneurysm, acute congestion and edema of the lungs, and arteriolar nephrosclerosis.

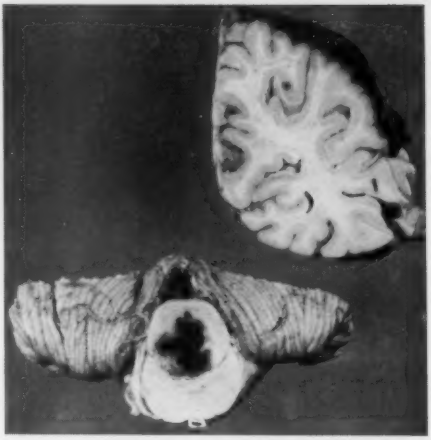

Fig. 4. (*Case 4*) Sections through the right parietal lobe and pons show the subdural hemorrhage and hemorrhage into the tegmentum.

Upon macroscopic examination of the brain, a subdural hematoma, 8 cm. in anteroposterior and 6 cm. in transverse diameter, was found overlying the right frontal and parietal lobes. A thin, brown, friable membrane was attached loosely to the inner surface of the right dural leaflet. Blood was found in the subarachnoid space over the right frontal lobe. On coronal section, the right centrum semiovale was moderately, diffusely swollen. The right cingulate gyrus and right uncus were herniated. Both cerebellar tonsils had moderate coning. A large hemorrhage involved the tegmentum of the pons and midbrain and, caudally, had ruptured into the fourth ventricle (Fig. 4). The major cerebral vessels showed extreme atherosclerosis without occlusions, and numerous small foci of old softening were noted in the basal ganglia.

Microscopic examination of hematoxylin-eosin preparations revealed the subdural hematoma to be recent. Red and white blood cells were well preserved. Actively proliferating fibroblasts were arranged in parallel rows adjacent to the internal surface of the dura. Hemorrhage had occurred into the underlying leptomeninges. The brain stem contained numerous, discrete or confluent, small, recent hemorrhages that occupied most of the tegmentum. Small arteries and arterioles in the brain substance and leptomeninges had greatly thickened media. Sometimes, the media had a smudged, deeply eosinophilic appearance, and, occasionally, medial thickening was sufficient to occlude the lumens of the vessels.

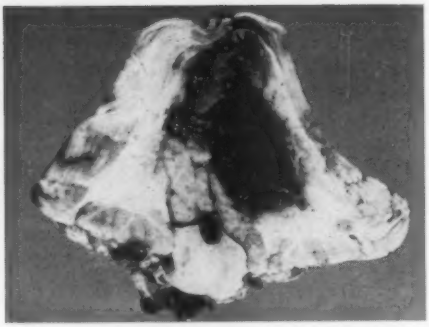

Fig. 5. (*Case 5*) The right cerebellar hemisphere and vermis are infiltrated by a large hemorrhage.

Case 5. A 59-year-old white man had crushing substernal pain on September 15, 1957, and was referred to Montefiore Hospital. A diagnosis of acute myocardial infarction was made on the basis of the clinical history, electrocardiographic changes, and elevated serum transaminase. The blood pressure at the time of admission was 200/100 mm. Hg and remained at hypertensive levels until death. With the onset of substernal pain, the patient was placed on sodium Warfarin. His course was uneventful until noon on September 20, when he vomited and appeared apprehensive. Two hours later, he was found dead in bed. The prothrombin time on the day of death was 45.4 sec., with a control of 12.

Pertinent extracranial postmortem findings were extreme generalized arteriosclerosis, left ventricular hypertrophy, an organizing hematoma in the wall of the right coronary artery, a fresh myocardial infarction involving the interventricular septum and wall of left ventricle, and acute and chronic pulmonary congestion.

Gross examination of the brain revealed a large hemorrhage replacing much of the right cerebellar hemisphere and impinging upon the roof of the fourth ventricle. The hemorrhage had ruptured through the dorsal surface of the vermis, staining the cerebellar leptomeninges with blood (Fig. 5). The third and fourth ventricles contained casts of blood. The major cerebral arteries had severe atheroma, with narrowing of the lumens.

Hematoxylin-eosin preparations showed a recent cerebellar hemorrhage. Morphologically, both erythro- and leukocytes were well preserved. The surrounding cerebellar cortex and white matter were normal except for slight edema.

In Cases 1 and 2, there can be little doubt on clinical grounds that repeated episodes of cerebral embolism had occurred. Recent cerebral emboli actually were found at autopsy in Case 1. In Case 3, postmortem examination disclosed a thrombus in the left auricle and an embolus astride the bifurcation of the abdominal aorta. The relationship of the emboli in the middle cerebral arteries to the subarachnoid hemorrhage in Case 1 was not clarified. Patients described by Scarrone and associates[5] and Gripe[6] are similar except that cerebral emboli were not found at autopsy. The massive cerebral hemorrhages in Cases 2 and 3 probably were preceded by hemorrhagic embolic infarcts. Admittedly, macroscopic and microscopic evidence of cerebral embolism was lacking. In any case, anticoagulants are believed to have been the ultimate cause of intracranial hemorrhage in Cases 1, 2, and 3. In Cases 4 and 5, severe hypertension prevailed. The rapidly fatal subdural hemorrhage in Case 4 also was attributed to anticoagulant therapy. No history of trauma was elicited, and the course was acute. The hemorrhage in the brain stem was the immediate cause of death and was secondary to increased intracranial pressure; however, anticoagulant therapy may have been a predisposing factor. In Case 5, a causative relationship between cerebellar hemorrhage and anticoagulation is suspected but the possibility of coincidence is admitted, since the patient was hypertensive. Prothrombin times in all 5 patients were prolonged to or beyond the upper limits of recommended therapeutic levels[3,4,7] at the time hemorrhage occurred.

REVIEW OF THE LITERATURE

Specific reference to 58 instances of intracranial hemorrhage during anticoagulant administration was found in the literature. Undoubtedly, many cases of intracranial hemorrhage coincident with anticoagulant therapy have not been reported. Lillie and associates[8] stated that extreme hypertension and a history of past "cerebrovascular accidents" were contraindications to the use of anticoagulants, as "fatalities in these circumstances have occurred in our experience." Nichol and associates[9] noted that mortality from cerebral hemorrhage in their series might have been higher "but undetected in some patients dying but not autopsied." Allen[10] reported that "many" patients died of cerebral hemorrhage at the Massachusetts General Hospital as a result of the use of heparin in bacterial endocarditis.

Of the 58 instances of intracranial hemorrhage cited above, 27 occurred in patients with bacterial endocarditis.[11–15] Intracerebral, intracerebellar, and diffuse subarachnoid hemorrhages all were described. The rationale for the use of anticoagulants in bacterial endocarditis was based on the assumption that fibrin and platelet deposition over the bacteria would be prevented, thus allowing direct access of leukocytes and sulfonamides to the organisms. Experience led to the recognition of the resultant high incidence of fatal cerebral hemorrhage, and bacterial endocarditis now is recognized as a contraindication to the use of anticoagulant drugs. Cerebral infarcts, presumably caused by emboli arising from vegetations on cardiac valves, may appear during the course of bacterial endocarditis; Cohen[11] suggested that the coincidence of cerebral infarction and anticoagulant-induced alteration of coagulability of the blood was responsible for the frequent occurrence of cerebral bleeding. Mycotic aneurysms were not found at autopsy in any of the patients reported.

Cerebral hemorrhage accompanying the use of anticoagulants[1,2,5–7,9,10,12,16–28] has been described in 31 patients without endocarditis, most of whom died. The table is a summary of these cases. The information tabulated is frequently fragmentary, since many accounts are incomplete. Several examples mentioned by Scarrone and associates[5] and Wright and associates[7] in which the possibility of a causal relationship between anticoagulant therapy and cerebral episodes was viewed with skepticism are not tabulated. Rainie's patient[29] is excluded, since clinical diagnosis of cerebral hemorrhage was made on tenuous grounds. Of the 31 cases analyzed, a recent focal lesion of the brain manifested by hemiplegia preceded the use of anticoagulants in 6. In none of these was a diagnosis of spontaneous intracerebral hemorrhage considered, nor do the accounts provided suggest such a diagnosis. Another 6 patients had 1 or more previous "cerebral thromboses" or "cerebrovascular accidents." Hypertension was mentioned specifically in 6 instances. Clinical and postmortem evidence of vascular anomalies and aneurysms was lacking in every patient described. The prothrombin and clotting times frequently were beyond the therapeutic range recommended by Wright and others. To anyone who has employed anticoagulants, the difficulties sometimes encountered in maintaining a consistently stable response require no emphasis.

DISCUSSION

Hypertension frequently is associated with spontaneous intracerebral hemorrhage. This association suggests caution in the use of anticoagulants in hypertensive patients. Of the 5 patients reported here, 1 was hypertensive and receiving anticoagulant therapy at the time of fatal intracerebellar hemorrhage. In 6 patients mentioned in the literature, hypertension and anticoagulant medication were associated with fatal intracerebral hemorrhage. The fact that most of these patients had prothrombin times beyond desirable therapeutic levels heightens the suspicion of a causal relationship between anticoagulant therapy and cerebral apoplexy; however, the number is small and the possibility of coincidence cannot be denied.

Another hazard in the use of anticoagulants is suggested by the fact that cerebral infarcts, particularly those due to emboli and carotid and basilar thrombosis, may be hemorrhagic. Administration of anticoagulants to a patient with a recent hemorrhagic cerebral infarct then would risk extensive cerebral hemorrhage. Clinical and experimental observations attest to the reality of this risk. Clinical evidence of cerebral infarction, which probably was due to emboli in several instances, preceded cerebral hemorrhage by three weeks or less in 6 reports summarized from the literature. In Cases 2 and 3 of this series, the conjecture that anticoagulant therapy caused massive hemorrhage into embolic infarcts seems reasonable. The accounts of intracerebral hemorrhage complicating anticoagulant therapy in patients with bacterial endocarditis might be advanced as examples of hemorrhage due to the same mechanism. Several experimental studies have demonstrated that administration of anticoagulants may provoke massive hemorrhage into brain infarcts in the dog.[30–32] In 2 investigations, the infarcts were produced by intracarotid injection of homologous blood clots. The hazard of hemorrhage appeared to be greatest within a two-week period after infarction.[32]

CEREBRAL HEMORRHAGE ACCOMPANYING ANTICOAGULANT THERAPY IN 31 PATIENTS

Author	*Age*	*Sex*	*Indication for Anticoagulation*	*Associated Conditions*	*Drug*	*Prothrombin Time*	*Hemorrhagic Complications*	*Autopsy*
Allen[10]	Elderly		Peripheral arteriosclerotic disease	——	Heparin	——	Cerebral hemorrhage	?
	Elderly		Peripheral arteriosclerotic disease	——	Heparin	——	Cerebral hemorrhage	?
Andersen[16]	44	F	Phlebitis	——	Dicumarol	No laboratory control	Hematuria; sudden onset of coma	Intracerebral hemorrhage
Duff and Shull[12]	43	F	——	Cerebral vascular accident ten months before hemorrhage; hypertension	Dicumarol	5%	Coma ending in death; meningeal signs; hemiplegia	No
	79	F	Femoral fracture	Previous cerebral vascular accident; hypertension	Dicumarol	Sudden fall to low level	Fatal cerebral hemorrhage	No
	36	F	Phlebothrombosis	——	Dicumarol	85 sec. (autopsy blood)	Left hemiparesis	Right parietotemporal hemorrhage; subarachnoid hemorrhage; petechiae left hemisphere
Fisher[1]	—	—	Repeated strokes (thromboses)	Hypertension	Dicumarol	8%	Fatal intracerebral hemorrhage	?
	—	—	Repeated strokes (thromboses)	Hypertension	Dicumarol	——	Fatal intracerebral hemorrhage	?
Foley and associates[17]	80	M	Hemiplegia	——	Heparin	——	Headache; coma six hours after heparin	Massive hemorrhage of brain
Gripe[6]	44	M	Cerebral embolus (clinical diagnosis)	Rheumatic heart disease; recent mesenteric embolus	Tromexan	80 sec.	Hematuria; meningeal signs; coma	Chronic rheumatic heart disease; diffuse subarachnoid hemorrhage
MacMillan and Brown[18]	—	—	Myocardial infarct	——	Heparin	Clotting time in therapeutic range	——	Hemorrhagic infarct of brain; mesenteric emboli
	—	—	Phlebothrombosis of leg	Previous cerebral thrombosis	Heparin	Clotting time in therapeutic range	——	Hemorrhagic infarct of brain
	—	—	Myocardial infarct	Previous cerebral embolus	Cyclocumarol	24%	——	Hemorrhagic infarct of brain
Martelli[19]	40	M	Phlebothrombosis of leg	——	Dicumarol	No laboratory control	Seizures; nonfatal subarachnoid hemorrhage	
Nichol and associates[9]			Death from cerebral hemorrhage attributed to long-term Dicumarol therapy in 4 patients with coronary atherosclerosis					

Martelli[19]	40	M	Phlebothrombosis of leg	——	Dicumarol	No laboratory control	Seizures; nonfatal subarachnoid hemorrhage	
Nichol and associates[9]			Death from cerebral hemorrhage attributed to long-term Dicumarol therapy in 4 patients with coronary atherosclerosis					
Olwin and Paul[20]	71	F	Retinal vein thrombosis	Hypertension	—	14% nineteen days before death	Fatal cerebral hemorrhage	?
Shapiro and associates[21]	—	F	Myocardial infarct	——	Dicumarol	50 sec.	Purpura; hematuria; coma, with fixed pupils, ending in death	No
Shlevin and Lederer[22]	79	F	Retinal vein thrombosis	Hypertension; heart failure	Dicumarol	84.4 sec.	Fatal multiple hemorrhages	Scattered subdural hemorrhages; hemorrhages of many organs
Stephens[23]	72	F	——	Multiple cerebral thrombi	—	——	Fatal cerebral hemorrhage	?
Vander Veer and associates[24]	59	M	Myocardial infarct	——	Tromexan	40%	Facial weakness; speech difficulty; reflex alteration	Hemorrhage of occipital lobe
Wright and Rothman[25]	46	M	Pulmonary infarct	Right hemiplegia, with clear cerebrospinal fluid, on admission	Dicumarol	40%	Hematuria; fatal cerebral hemorrhage, with bloody cerebrospinal fluid	No
Wright and associates[2,5,7,27] and McDevitt[26]	—	—	Massive myocardial infarct	Hypotension and oliguria	Dicumarol and Paritol	54 sec.	Signs of cerebral hemorrhage. (died)	No
	—	—	Massive myocardial infarct	Hypotension and oliguria	Dicumarol and Paritol	22 sec. (clotting time 160 min.)	Signs of cerebral hemorrhage. (died)	No
	44	M	Cerebral embolus	Chronic rheumatic heart disease	Tromexan	69 sec.	Nuchal rigidity; coma	Mitral stenosis; auricular thrombi; renal infarcts; diffuse subarachnoid hemorrhage
	53	F	Repeated cerebral emboli	Chronic rheumatic heart disease; myocardial infarct	Depo-heparin	——	Signs of cerebral hemorrhage	Anemic infarcts of both hemispheres; hemorrhage of left internal capsule
	—	—	Cerebral thrombosis	Atherosclerosis	Intravenous heparin	——	Signs of cerebral hemorrhage	Cerebral hemorrhage, with rupture into ventricular system
	—	—	Cerebrovascular disease; probable cerebral embolus	——	—	——	Headache, disorientation; nonfatal subarachnoid hemorrhage	
	—	—	Cerebrovascular disease; right hemiplegia	——	—	——	Stiff neck; nonfatal subarachnoid hemorrhage	

The evidence advanced above appears to indicate that use of anticoagulant drugs is accompanied by an appreciable risk of cerebral hemorrhage in patients with [1] hypertension and [2] recent cerebral infarction, particularly that due to emboli. Anticoagulant therapy has been advised for patients with the "intermittent insufficiency" syndromes accompanying occlusive disease of the carotid and basilar arteries and recurrent cerebral embolism. Patients with carotid and basilar disease frequently are hypertensive. Patients of both groups in which anticoagulants are advocated are prone to cerebral infarcts during treatment and, in our view, risk the complication of massive, fatal, cerebral hemorrhage. A recent report of McDevitt and associates[2] is germane to these remarks. A group of 100 patients, most of whom had cerebral emboli, were treated with anticoagulants for cerebrovascular disease. Duration of treatment was twenty-four hours to ten years. Follow-up was done for more than six years in 30 patients. At the time of the report, 5 patients had cerebral hemorrhage attributable to anticoagulant therapy. In 3, the cerebral hemorrhage was fatal. This is a formidable rate of complication in a series which remains under study.

It is not the purpose of this article to deny the value of anticoagulants in treating cerebrovascular disorders. Clinical studies already mentioned suggest that anticoagulants are of value in selected types of cerebrovascular disease. Our purpose is to indicate that, in certain situations, cerebral hemorrhage may complicate anticoagulant therapy and often is fatal.

Accurate estimation of the frequency and importance of this complication requires further experience with large groups of patients. In the meantime, anticoagulants should be used with caution in patients with hypertension or recent strokes.

SUMMARY

Descriptions of 5 cases of intracranial hemorrhage accompanying anticoagulant therapy are given, and the literature on the subject is reviewed. Caution is advised in the use of anticoagulants in patients with hypertension or recent cerebral infarctions, particularly those due to embolism.

ADDENDUM

Since completion of this paper, the authors have observed an instance of fatal hemorrhage into the medulla oblongata in a hypertensive male who received Dicumarol. At the time of onset of symptoms, the prothrombin time was 21 sec. with a control of 11.

Recently, Vastola and Frugh[33] have reported 4 cases of cerebral hemorrhage in patients with recent occlusive cerebrovascular lesions who were treated with coumarin compounds. In each of their patients, hemorrhage occurred while the prothrombin time was in the therapeutic range. Nathanson and co-authors[34] have described acute subdural hematoma in 3 patients receiving anticoagulants (see Case 4 of this article). There was no evidence of trauma. At least 1 patient was hypertensive. Brief allusion to other examples of cerebral hemorrhage attributed to anticoagulant therapy has appeared in other reports.[35,36]

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Tryptophan metabolism in porphyria, schizophrenia, and a variety of neurologic and psychiatric diseases

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PATIENTS WITH ACUTE hepatic porphyria frequently have an increased urinary excretion of zinc, while patients with mixed and chronic hepatic porphyria frequently excrete increased quantities of copper or both copper and zinc.[1-3] Administration of chelating agents such as 2, 3-dimercaptopropanol (BAL) and ethylenediaminetetraacetic acid (EDTA) to these patients was associated with a zinc diuresis in the patient with acute porphyria and a copper, and sometimes a zinc, diuresis in patients with chronic and mixed forms of porphyria. Associated with chelation, a considerable improvement frequently occurred in the clinical condition of the patient.[1-5] These observations led to the suggestion that, in hepatic porphyria, the symptomatology may be related, in part, to an imbalance of polyvalent cations and an associated blocking effect on various metalloenzyme systems.

Previous studies from these laboratories have indicated that most patients with acrosclerosis had abnormal tryptophan metabolism.[6,7] The type of abnormal tryptophan metabolism observed in patients with acrosclerosis suggested that a deficiency in pyridoxine might exist in these patients, but vitamin B_6 in large amounts failed to correct the abnormal tryptophan metabolism in many of them.[7]

Since Metzler, Ikawa, and Snell[8] have suggested that the active form of pyridoxal phosphate may be a chelate with a polyvalent cation, the occurrence of an imbalance in tissue metal ions might be responsible for the apparent functional deficiency of vitamin B_6 in acrosclerosis. This possibility was supported by the fact that administration of EDTA produced a considerable increase in the urinary excretion of copper and zinc by patients with acrosclerosis, an associated clinical improvement of the patients, and a considerable degree of correction of the abnormal tryptophan metabolism.[6,7] Studies elsewhere have indicated that the urinary excretion of several other polyvalent cations may be increased by intravenous administration of EDTA.[9]

Because of the evidence for an abnormality in polyvalent cation excretion by patients with porphyria, it was decided to determine whether or not they, like the patients with acrosclerosis, might also have a disturbance in tryptophan metabolism. Patients with schizophrenia were studied because several of the patients with porphyria showed schizophrenic symptomatology and, in fact, some of the porphyric patients had previously been considered schizophrenic. Patients with other neurologic or psychiatric conditions were studied in a similar manner to determine whether they might have some defect in the metabolism of tryptophan. In a few instances, the effects of chelating agents and other drugs were studied for their influence on the patient's metabolism of tryptophan.

In these studies, tryptophan metabolism was evaluated by determination of 9 urinary metabolites of this amino acid. The advantages

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of measuring several of these metabolites, as compared with measurements of a single metabolite such as xanthurenic acid, have been emphasized previously[7] and were demonstrated again in the present report. The recent development of convenient analytic methods for several of the urinary metabolites of tryptophan[10-13] has made studies of this type possible.

The present report presents evidence that most of the patients with porphyria failed to metabolize a 2 gm. dose of tryptophan in a normal manner and that the urinary-excretion pattern of metabolites resembled that seen in patients with acrosclerosis. A few of the patients with schizophrenia had similar urinary excretion patterns of metabolites, but most of the remaining patients with schizophrenia, unlike the majority of patients with porphyria, excreted less than the expected amount of tryptophan metabolites. A few of the patients with other types of psychoses failed to metabolize a loading dose of tryptophan in a normal manner, but the majority of patients with neurologic diseases had a normal response in these metabolic studies.

EXPERIMENTS

Subjects. The patients with porphyria have been previously categorized and included patients with peripheral neuropathy, transverse myelitis, schizophrenic-like psychosis, and, in the mixed and chronic porphyric group, cutaneous symptomatology. Of the porphyric patients, 4 were considered to belong to the paraporphyric group described previously.[3] The paraporphyric patients included 3 who clinically resembled the acute porphyric patients, of whom 1 was in remission; another resembled clinically the mixed porphyric patient.

The schizophrenic patients had been referred to the Psychiatry Department at the University Hospitals by their local physicians and included 9 patients who were experiencing their first psychotic episode. The remainder of the group were in more chronic phases of the disorder. The patients with the other types of psychoses, as well as those with various neurologic disorders, were also referred to the Psychiatry or Neurology Departments at the University Hospitals by their local physicians. The subjects with muscular dystrophy were individuals in whom the disease had started rather late in life. Of the subjects, 3 were mature adults; 2 were about 14 years of age.

Half of the control subjects were laboratory and hospital personnel who had no known disease. The remainder of the control subjects were patients admitted to the University Hospitals for conditions which seemed unlikely to have metabolic implications, such as varicose veins or hernias, and a few were studied just before discharge from the hospital following treatment for minor illnesses. Since there seemed to be no indication that the hospitalized patients metabolized tryptophan differently from the subjects with no known disease, the control subjects were placed in one group.

A single twenty-four-hour urine collection was made, and the patient was then given 2 gm. of L-tryptophan in half-gram tablets and a second twenty-four-hour urine specimen collected. Studies were often repeated during or after treatment. Urine collections were made under toluene in amber bottles and were refrigerated until analyzed.

Analytic methods. Determinations of urinary *N*-methyl-2-pyridone-5-carboxamide (pyridone), aromatic amine fraction A, anthranilic acid glucuronide, o-aminohippuric acid, anthranilic acid, kynurenine, N^{α}-acetyl-kynurenine, and 3-hydroxykynurenine were made as previously described.[10-12] In these studies, aromatic amine fraction A was calculated as indican rather than as anthranilic acid[11] because indican was the chief reactant in this fraction.[14] This change in calculations resulted in values which were, in terms of micromoles, 7.6 times the values obtained when anthranilic acid was the reference standard. In a few instances, xanthurenic acid was determined by a colorimetric method,[15] but the majority of determinations were done with a fluorometric procedure[13] which was also used for most of the kynurenic acid determinations. Paper chromatography was done on all aromatic amine fractions to provide a qualitative check on the quantitative determinations.[11,16] In this manner, we were certain that the metabolites determined were actually present in the samples and that other substances were not present which might give a similar color response.

TABLE 1

URINARY EXCRETION OF TRYPTOPHAN METABOLITES, ZINC, AND COPPER BY PATIENTS WITH PORPHYRIA AS COMPARED WITH A GROUP OF SUBJECTS WITH NO KNOWN DISEASE

(The number of patients with the various types of porphyria who clearly had abnormal tryptophan metabolism were as follows: acute porphyria, 6; acute porphyria in remission, 3; mixed porphyria, 4; and chronic porphyria, 0. The patient with chronic porphyria did, however, excrete an abnormal amount of acetylkynurenine following ingestion of tryptophan.)

Diagnosis	*Number of patients*	*Before (B) or after (A) tryptophan*	*Urinary tryptophan metabolites, micromoles per twenty-four hours†*									*Urinary zinc and copper, mg./liter*	
			MPCA	*KA*	*XA*	*A*	*AAG*	*o-AH*	*AcK*	*K*	*HK*	*Zn*	*Cu*
Acute porphyria	6	B	75 24–156	12 8–19	11 6–17	304 74–773	5 2–7	21 10–36	12 6–21	19+ 10–31	41 9–90	1.52 .25–4.20	.12 .05–.21
		A	130 28–248	202+ 79–630	96+ 43–131	366 136–775	12 5–24	100 16–359	85+ 22–198	407+ 29–1376	312+ 71–800		
Acute porphyria, remission	6	B	69 54–89	13 9–27	15 9–33	380 243–797	3 2–6	18 12–26	10 5–22	12 3–21	29 12–43	0.36 .15– .80	.08 .04–.10
		A	91– 48–112	90 31–178	79 7–161	436 176–708	7 5–11	41 32–56	35 10–122	99 31–121	97 35–175		
Mixed porphyria	5	B	79 32–213	14 4–43	17 7–48	396 235–730	7 4–10	31 15–72	26 15–64	31+ 24–46	38 23–56	0.82 .47–1.55	.17 .08–.33
		A	97 65–137	92+ 48–135	55 15–95	446 286–574	13 6–25	58 38–89	66+ 25–102	211+ 71–515	175 38–455		
Chronic porphyria	1	B	110	13	11	414	5	19	8	11	25	.80	.15
		A	147	98	50	352	19	60	63	82	68		
Controls‡	29	B	95 34–149	11 2–19	9 4–15	387 175–699	5 2–9	25 15–36	12 6–22	13 6–21	28 11–61	* –	* –
		A	135 74–213	60 30–99	39 18–71	412 167–760	8 2–19	47 23–94	18 8–32	28 9–83	52 7–76		

– Indicates values significantly lower ($P < 0.02$) than control subjects.

+ Indicates values significantly higher ($P < 0.02$) than control subjects.

†The abbreviations used in this table were as follows: MPCA = N-methyl-2-pyridone-5-carboxamide; KA = kynurenic acid; XA = xanthurenic acid; A = aromatic amine Fraction A; AAG = anthranilic acid glucuronide; o-AH = o-aminohippuric acid; AcK = acetylkynurenine; K = kynurenine; HK = hydroxykynurenine.

The same abbreviations were used in the other tables.

‡XA and HK have been determined in only 8 and 11 of these control subjects, respectively.

*Zinc and copper excretion levels were not obtained for these control subjects. However, for other normal subjects the normal values for urinary zinc and copper have been 0.5 and 0.04 mg. per liter, respectively.[1]

The creatinine content of most of the urine samples was determined in an effort to evaluate the extent to which the urine collections had been made in a quantitative manner.

The methods of determination of zinc, copper, delta-aminolevulinic acid, and porphyrins have been described.[1]

The data obtained for tryptophan metabolites in the urine of patients with acute porphyria, acute porphyria in remission, and mixed porphyria and in urine of schizophrenic patients with abnormally high excretions of 2 or more tryptophan metabolites and in the urine of other schizophrenic patients were compared with comparable data for the control subjects. In the statistical analyses, the data for basal and posttryptophan periods were compared with the standard t test and the probability (P) values were obtained.[17] Because of the large number of P values obtained in this study and the wide range of values in some groups, only P values of 0.02 or less were considered significant, rather than the usual limit of 0.05.

RESULTS

The interrelationships of the metabolites under consideration in this study have been diagrammed (Fig. 1). All of the metabolites considered in this study are products of the conversion of tryptophan to niacin.

Compared with the controls, the patients with acute porphyria excreted significantly more kynurenine in the urine before and after tryptophan supplementation (Table 1). Following tryptophan supplementation, these patients also excreted significantly more kynurenic acid, xanthurenic acid, acetylkynurenine, and hydroxykynurenine than the controls.

The patients with acute porphyria in remission, however, had a pattern of urinary tryptophan metabolites which did not differ significantly from the pattern in the controls except for a lower excretion of the pyridone after tryptophan loading. The patients with mixed porphyria excreted significantly more kynurenine before and after tryptophan supplementation than did the controls, and, following supplementation with the amino acid, these patients also excreted increased quantities of kynurenic acid and acetylkynurenine. The patient with chronic porphyria metabolized tryptophan in a normal manner except for an abnormally high level of acetylkynurenine in the urine after administration of tryptophan.

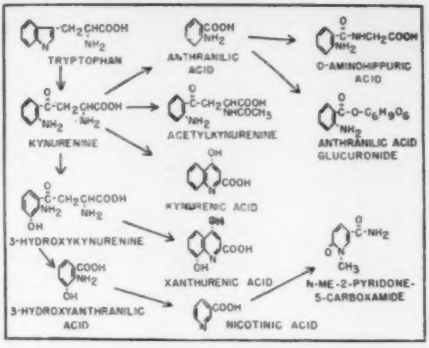

Fig. 1. An abbreviated diagram showing the metabolic interrelationships of the products formed in the conversion of tryptophan to niacin and N-methyl-2-pyridone-5-carboxamide, the chief metabolite of niacin in man. This diagram has been published previously.[7]

Most of the patients with acute porphyria and 2 of the 5 patients with mixed porphyria excreted abnormally high levels of zinc (Table 1). Urinary copper was increased in most of the porphyria patients.

Of the patients with schizophrenia, 6 showed distinctly abnormal tryptophan metabolism and the other 13 metabolized the amino acid in a normal manner. The data for these 2 groups were presented separately as the average and range of values — as were the data for the controls and the patients with porphyria (Table 2). Both groups of schizophrenic patients excreted significantly less of the pyridone before or after tryptophan ingestion, compared with the controls. The patients with abnormal metabolism excreted significantly more kynurenic acid, o-aminohippuric acid, acetylkynurenine, kynurenine, and hydroxykynurenine after tryptophan than did the controls. The other group of schizophrenic patients excreted significantly less kynurenic acid and o-aminohippuric acid before or after tryptophan supplementation and less kynurenine after tryptophan as compared with the controls.

These comparisons may be made more readily by inspection of Figures 2 and 3, where

0.5 and 0.04 mg. per liter, respectively.

TABLE 2

URINARY EXCRETION OF TRYPTOPHAN METABOLITES BY PATIENTS WITH SCHIZOPHRENIA

(The patients were divided into 2 groups: 6 patients who had an abnormally high excretion of 2 or more metabolites, and 13 patients whose excretions of the metabolites were normal or below the range of the controls for all metabolites. Zinc and copper determinations were done on very few of these patients, and only 1 patient was chelated.)

Number of patients	Before (B) or after (A) tryptophan	MPCA	KA	XA	A	AAG	o-AH	AcK	K	HK
6	B	41– 16–55	14 5–21	11 3–18	356 190–684	4 1–6	22 12– 34	14 8– 25	17 7– 32	24 11– 38
	A	80– 9–92	157+ 41–278	44 13–77	440 213–737	13 3–30	81+ 32–169	90+ 24–344	328+ 68–1123	134+ 59–223
13	B	48– 30–73	8– 4–12	10 4–21	313 132–535	5 2–10	17– 9–21	10 5–17	9 6–18	21 15–69
	A	72– 24–115	34– 10–60	29 8–77	346 139–770	7 3–11	30– 11–45	13 4–28	23– 7–60	38 15–69

– Indicates values significantly lower ($P \leq 0.02$) than control subjects.
+ Indicates values significantly higher ($P \leq 0.02$) than control subjects.

Fig. 2. Patterns of tryptophan metabolites in the urine before tryptophan administration. The number of subjects studied in each group is indicated in parentheses opposite the term indicating the classification of the groups. The terms normal and abnormal, as used in connection with schizophrenia, apply to the metabolic response to tryptophan as indicated in the text. The black portions of the bar graphs represent the average values for the particular metabolite, and the colorless bars superimposed on the black bars indicate the upper and lower limits of the range of values. (Since there was only 1 subject in the chronic porphyria group, no range was shown.) The scales are in micromoles of metabolite excreted in twenty-four hours. Because the basal urinary excretion of MPCA and A were so large, separate scales were necessary for these components. The abbreviations used were: K, kynurenine; AcK, acetylkynurenine; o-AH, o-aminohippuric acid; KA, kynurenic acid; HK, hydroxykynurenine; XA, xanthurenic acid; AAG, anthranilic acid glucuronide; MPCA, pyridone; and A, indican.

the results were presented graphically. The graphs indicate the similarity in the abnormal response to tryptophan observed in the patients with porphyria and in patients with schizophrenia with abnormal metabolism. The normal response to tryptophan in the other 13 schizophrenic patients was actually subnormal in that they excreted significantly less of some of the metabolites than did the controls. A few of the controls had a minimal response to tryptophan, but this flat response to

the metabolic studies is very common in this group of schizophrenic patients.

Of the schizophrenic patients in the abnormal group, 2 were men, while of the subjects in the normal group, 6 were men. Four of the 6 subjects in the abnormal group and 5 of the 13 subjects in the normal group were considered to be acutely ill in that their admissions represented their first hospitalization for schizophrenia. The remaining subjects had been treated on one or several occasions for their schizophrenic psychoses.

The patients with a variety of psychoses showed a high incidence of abnormal tryptophan metabolism (Table 3). The pattern of urinary metabolites excreted by these subjects after administration of the loading dose of tryptophan was similar to that seen in patients with porphyria. Thus, in most instances, the chief urinary metabolite of tryptophan was kynurenine and elevated amounts of hydroxykynurenine, acetylkynurenine, kynurenic acid, and somewhat elevated amounts of xanthurenic acid were observed in the urine. As in the patients with porphyria, good correlation did not exist between urinary zinc or copper and tryptophan metabolism. The patient with the postpartum psychosis was studied again following administration of sedative insulin and electroconvulsive therapy with recovery.

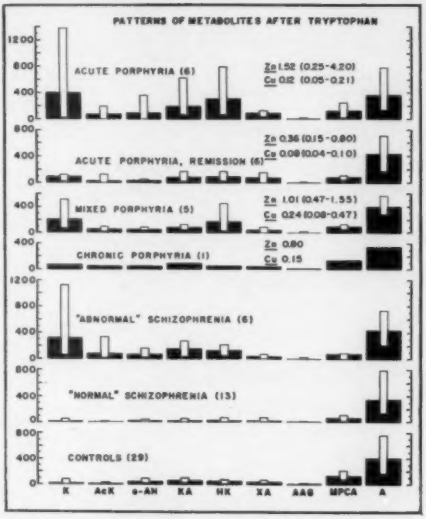

Fig. 3. Patterns of metabolites in the urine after the ingestion of 2 gm. of L-tryptophan by patients with porphyria and schizophrenia and by a group of 29 controls. The data were presented as in Figure 2, and the same abbreviations were used. The average urinary excretion of zinc (Zn) and copper (Cu) for the patients with porphyria has been given on the graph in milligrams per liter of urine. The range of values has been shown in parentheses.

TABLE 3
URINARY EXCRETION OF TRYPTOPHAN METABOLITES, ZINC, AND COPPER BY PATIENTS WITH A VARIETY OF PSYCHOSES

No.	Sex	Diagnosis	Before (B) or after (A) tryptophan	Urinary tryptophan metabolites, micromoles per twenty-four hours									mg./liter of urine	
				MPCA	KA	XA	A	AAG	o-AH	AcK	K	HK	Zn	Cu
1.	F	Reactive depression	B	15	5	11	296	1	12	13	14	16		
			A	27	124	90	495	5	44	89	292	106	.23	.06
2.	F	Involutional depression	B	30	11	73*	228	3	30	9	11	20		
			A	54	106	84*	213	10	79	34	270	112	.16	
3.	F	Organic psychosis	B	86	15	65*	433	6	29	9	31	34		
			A	151	123	50*	418	10	73	19	248	90		
4.	M	Paranoid psychosis	B	65	20	106*	471	10	38	20	31	61		
			A	118	133	97*	692	18	79	42	177	155	1.08	.07
5.	F	Postpartum psychosis	B	18	7	6	270	4	17	17	15	12		
			A	15	100	64	191	4	32	67	138	82	.294	.08
6.	M	Toxic psychosis	B	94	11	16	612	8	36	22	25	100		
			A	108	29	26	53	10	44	24	32	127	1.7	.20
7.	M	Alcoholic hallucinosis, chronic	B	26	6	7	242	3	12	8	9	8		
			A	78	75	93	298	7	25	17	46	41	.48	.10
8.	M	Organic psychosis	B	72	11	9	369	6	56	18	32	41		
			A	193	22	19	437	8	67	21	96	65	2.28	.11

*These values for XA were obtained by a colorimetric method and were normal for this method of analysis.

TABLE 4

URINARY EXCRETION OF TRYPTOPHAN METABOLITES BY PATIENTS WITH A VARIETY OF NEUROLOGIC CONDITIONS

(The data for 5 patients with adult form of muscular dystrophy have been averaged, and the range of values has not been given because all were within the range for the controls (Table 1), except that 1 patient excreted a slightly elevated level of acetylkynurenine and kynurenine and 1 excreted a slightly elevated amount of hydroxykynurenine.)

No.	Sex	Diagnosis	Before (B) or after (A) tryptophan	Urinary tryptophan metabolites, micromoles per twenty-four hours								
				MPCA	KA	XA	A	AAG	o-AH	AcK	K	HK
1.	M	Uncontrolled epilepsy	B	15	5	5	95	2	11	8	13	8
			A	12	42	17	85	5	33	6	23	25
2.	M	Chronic epilepsy	B	88	10	17	653	10	50	39	40	38
			A	39	68	44	970	14	67	32	58	85
3.	F	Encephalomyelitis	B	72	11	57*	266	2	19	7	9	20
			A	99	109	75*	334	7	54	17	66	67
4.	F	Amyotrophic lateral sclerosis	B	157	13	53*	296	4	24	7	9	3
			A	217	26	47*	388	11	54	9	22	36
5.	M	Friedreich's ataxia	B	55	7	6	186	3	25	5	11	27
			A	116	47	35	193	5	29	19	18	22
6.	—	Muscular dystrophy	B	84	10	29*	315	4	21	9	11	33
			A	164	70	42*	324	5	50	20	50	87

*These values for XA were obtained by a colorimetric method and were normal values for this method of analysis.

Following recovery, this patient metabolized tryptophan in a normal manner.

Each of the patients with a variety of neurologic diseases metabolized tryptophan normally except as noted in the heading to Table 4. It was of particular interest that the 2 patients with epilepsy had normal tryptophan metabolism.

CASE REPORTS

Case 1, a 17-year-old girl, was admitted to University Hospitals on November 6, 1957. Second oldest in a family of 6 children, she had been quite upset three years before at the pregnancy and forced marriage of her older sister. Generally shy and overly concerned with cleanliness, the patient had been preoccupied with social experiences outside of school which included a liaison with an older man. Onset of the psychotic symptoms followed the flu; the patient had insomnia, stopped eating, and developed ideas of reference.

The first study on tryptophan metabolism was done six days after admission — at which time she was receiving 25 mg. of chlorpromazine two to three times daily. On November 20, 1957, the patient became more confused and self-derogatory and expressed delusional feelings. Brief subcoma insulin aggravated her psychosis. During this period, the tryptophan metabolism study was repeated with pyridoxine supplements.

The test for fecal protoporphyrin, which was positive on several occasions after admission, became markedly positive on November 29, 1957, following administration of 3 gr. of amytal at bedtime. On December 4, 1957, iproniazid therapy—50 mg. daily—was begun and was accompanied by an explosive increase in psychotic symptoms with hebephrenic, delusional, and hallucinatory phenomena.

On December 10, 1957, BAL therapy—0.5 cc. intramuscularly 4 times a day—was initiated. The following morning, the patient was oriented but seemed depressed. At this time, and on subsequent days, she showed what seemed to be improvement in affective response accompanied by considerable abreaction during which supportive psychotherapy was rendered. With this behavior, occasional reactivations of delusional material occurred.

On December 13, 1957, BAL therapy was discontinued and on December 15, 1957, 40 mg. of azacyclonol hydrochloride and 25 mg. of chlorpromazine four times daily were begun on an empiric basis. Her condition continued to improve, and, by December 21, 1957, she seemed completely well. She was discharged on December 23, 1957, and tryptophan studies were repeated just prior to discharge.

Normal fecal protoporphyrin excretion was noted toward the end of her hospitalization. Delta-aminolevulinic acid determinations during hospitalization were slightly elevated to 3.6 mg. per liter, while porphobilinogen was not demonstrated. The coproporphyrin values ranged from 2 to 4 plus, with negative uroporphyrin excretion. The electroencephalogram was normal.

Follow-up evaluation on March 24, 1958, revealed that the patient had gone back to school on a reduced schedule. The patient had complete insight into the delusional material expressed during hospitalization and seemed to be taking realistic steps toward improving her interpersonal relationships. Though still slightly flattened, her affect seemed appropriate and outpatient psychotherapy was recommended. The patient was instructed to avoid use of barbiturates, drugs, and alcoholic beverages.

This patient appeared to represent a paraporphyric[3] patient in whom the metabolic disturbance paralleled the psychotic state. She was considered to be a probable porphyric-schizophrenic. Exaggeration of psychotic symptoms was noted with iproniazid therapy, and administration of BAL seemed ineffective in aborting hebephrenic behavior apparently induced or aggravated by iproniazid. Supportive psychotherapy with alleviation of guilt feelings was important in bringing about clinical recovery.

Case 1 had abnormal tryptophan metabolism during the first study, at which time she was psychotic and receiving chlorpromazine (Table 5). Studies on 2 other patients before and during administration of chlorpromazine indicated that this drug, at least in the dosage level used, had no effect on the metabolism of tryptophan. Thus, it was unlikely that chlorpromazine was responsible for the abnormal tryptophan metabolism observed in this patient with porphyria. When the patient was given 100 mg. of pyridoxine hydrochloride per day, her tryptophan metabolism improved in that urinary excretion of kynurenine and hydroxykynurenine decreased. However, excretion of kynurenic acid failed to return to normal levels. After recovery from her psychosis following treatment with BAL and, later, azacyclonol and chlorpromazine, she metabolized tryptophan in a normal manner.

Case 2 was previously summarized[1] and was characterized by development of complete tetraplegia due to peripheral neuropathy following an abdominal exploratory operation under intravenous barbiturate anesthesia. The patient was made worse by administration of ACTH.

The patient was psychotic throughout the early course of his acute porphyria, and the psychosis was immediately aborted by chelation. Clinical improvement of neurologic symptoms began only after chelation. Before chela-

TABLE 5
EFFECTS OF PYRIDOXINE OR TREATMENT ON THE METABOLISM OF TRYPTOPHAN BY CASES 1 AND 2

Subject	Date	Before (B) or after (A) tryptophan	Micromoles of urinary tryptophan metabolites excreted per twenty-four hours									Remarks
			MPCA	KA	XA	A	AAG	o-AH	AcK	K	HK	
Case 1 (acute porphyria)	11/12/57	B	81	8	11	74	2	10	6	10	10	Before treatment
	11/13/57	A	186	147	131	136	5	16	45	322	141	
	11/27/57	B	144	13	15	233	4	12	8	13	18	Receiving 25 mg. pyridoxine hydrochloride q.i.d.
	11/28/57	A	180	127	80	178	9	34	40	96	63	
	12/22/57	B	56	10	8	197	2	14	8	11	12	After treatment and recovery
	12/23/57	A	103	69	28	114	6	27	39	57	44	
Case 2 (acute porphyria in remission)	2/25/58	B	85	21	24	311	2	14	5	10	39	Before pyridoxine
	2/26/58	A	112	178	107	568	6	48	30	141	100	
	2/27/58	B	160	33	28	380	4	25	10	17	43	Receiving 25 mg. pyridoxine hydrochloride q.i.d.
	2/28/58	A	157	186	82	562	8	81	34	87	100	

tion, urinary zinc excretion was 36 times normal, higher than in any other porphyric patient studied, and zinc diuresis fell to normal limits despite continued chelation.

At the time that his tryptophan metabolism was studied on February 25, 1958, fifteen months had elapsed since his discharge from the University Hospitals and tryptophan studies were done on an outpatient basis.

Urinary zinc excretion at the time of study was .26 mg. per liter, while the excretion of copper was .06 mg. per liter and the fecal protoporphyrin was 3 plus. Although the patient was clinically well so far as his psychosis and neurologic condition were concerned—he had suffered no relapse in neurologic or psychiatric symptoms in the past fifteen months—his tryptophan metabolism was still somewhat abnormal (Table 5). The administration of pyridoxine hydrochloride at a level of 100 mg. per day failed to correct his tryptophan metabolism, although the excretion of kynurenine dropped to the upper limits of the normal range. This response to vitamin B_6 was identical with the type of response previously observed in patients with scleroderma given supplements of vitamin B_6.[7]

DISCUSSION

The results obtained indicate that certain psychotic patients and many patients with porphyria failed to metabolize kynurenine and 3-hydroxykynurenine in a normal manner. These tryptophan metabolites and closely related products were excreted in the urine in abnormally large amounts after ingestion of a loading dose of this essential amino acid by these patients. In terms of existing knowledge, this type of abnormal tryptophan metabolism might be expected in animals with a functional deficiency of pyridoxine.

Apparently, various types of disorders of tryptophan metabolism occur in man,[18] and the disorder that most nearly resembles porphyria is seen in acrosclerosis.[7,18] The disorders of tryptophan metabolism in acrosclerosis and porphyria did not respond to pyridoxine supplementation. No evidence exists that pyridoxine supplementation was of value from a clinical standpoint in patients with porphyria or acrosclerosis.[7] However, both of these conditions responded clinically and biochemically to EDTA supplements and to EDTA plus pyridoxine or to BAL. Thus, an apparent functional deficiency of pyridoxine responded not to pyridoxine but to the chelating agents, EDTA or BAL.

The apparent pyridoxine-like activity of EDTA and BAL on tryptophan metabolism cannot be explained in terms of existing knowledge, at least, as an indication of vitamin B_6 activity of these chelating agents. Furthermore, administration of large amounts of EDTA to human subjects has been associated with the development of lesions in the skin which resemble those seen in pyridoxine deficiency, and these lesions responded to the administration of vitamin B_6.[9,19,20] Thus, administration of EDTA will alleviate an apparent vitamin B_6 deficiency in some human subjects and, in others, will apparently induce pyridoxine deficiency. This suggests that pyridoxine may not function properly in the presence of an imbalance of metal ions. If this were true, one could readily understand the production of a pyridoxine deficiency and of pyridoxine activity by a chelating agent, depending upon whether an imbalance of cations was created or corrected, respectively, by the chelating agent.

Evidence suggests that pyridoxal phosphate, the active form of pyridoxine, may require the participation of a polyvalent cation. Metzler, Ikawa, and Snell[8] have demonstrated that pyridoxal phosphate, a substrate, and some polyvalent cation may react to form a product. They suggested that this may indicate participation of some polyvalent cation in the reactions of pyridoxal phosphate in vivo.

In both scleroderma and porphyria, evidence exists of disturbance in the tissue levels of polyvalent cations. In scleroderma, deposition of minerals occurs in the soft tissues[21] and, in porphyria, an increase occurs in the excretion of zinc and often copper in the urine.[1-3] Possibly, in the face of an imbalance of polyvalent cations, the metal ion which has become complexed by the pyridoxal phosphate moiety may not be the metal which normally functions with the cofactor. This might be expected to decrease the functional capacity of the vitamin B_6 in the tissues. The administration of large amounts of vitamin B_6 might fail to return the functional level of pyridoxal phos-

phate to normal because the administered vitamin would face the same competition for cations. The development of symptoms suggestive of pyridoxine deficiency in human subjects to whom these chelating agents have been administered in the presumed absence of an imbalance of polyvalent metal cations might be explained by elimination of large quantities of the cation which normally functions with pyridoxal phosphate. The activity of the cofactor is reduced through loss of the normal metal ion or its displacement by another metal ion by competition—creation of an imbalance.

Certain in vitro studies suggested that such interaction of polyvalent cations may influence reactions catalyzed by pyridoxal phosphate. Thus, Yanofsky[22] found that Neurospora D-serine dehydrase required pyridoxal phosphate and that the enzyme system was inhibited by phosphate, citrate, cysteine, cyanide, or 8-hydroxyquinoline. These inhibitions suggested that the enzyme system was metal-activated, and magnesium could partially reverse some of these inhibitors. The enzyme system was also partially inhibited by cobalt, copper, or zinc, and this inhibition was also partially reversed by magnesium. Furthermore, inhibition by cobalt, copper, or zinc was only partially reversed by addition of large amounts of pyridoxal phosphate.

A corollary of the suggestion proposed above would be that at least some of the symptoms in porphyria, scleroderma, or both may be directly or indirectly the results of functional deficiencies of pyridoxine in the tissues. In this respect, Kugelmass[23] stated that pyridoxine deficiency may be associated with weakness, nervousness, irritability, abdominal pain, and difficulty in walking. These symptoms, as well as many others, have been observed in patients with porphyria.[1,3] Furthermore, administration of isoniazid, a known antagonist of vitamin B_6, occasionally is associated with development of psychoses or peripheral neuropathy[24–26] in patients treated for tuberculosis, and peripheral neuropathy may be prevented by pyridoxine.[27,28]

Vilter and his associates[29] noted that, in some human subjects, administration of deoxypyridoxine was associated with nausea, vomiting, lethargy, somnolence, or confusion. Some of their patients also experienced seborrheic dermatitis, intertrigo, and a hyperpigmented, scaling and pellagra-like dermatitis on the arms and legs. Although seborrheic dermatitis has not been noted in our patients with porphyria, the other dermatologic signs associated with the administration of deoxypyridoxine to human subjects have been observed in the porphyria patients.[1,3] Furthermore, deoxypyridoxine, isoniazid, and similar drugs capable of antagonizing vitamin B_6 have been shown to produce convulsions in various species of animals. These convulsions resemble those which have been observed in vitamin B_6 deficient animals[30] and in the porphyric patients.[1–3] Thus, a number of the symptoms in porphyria have been seen in patients with disturbed pyridoxine metabolism.

The type of disturbance of tryptophan metabolism observed in the patients with tuberculosis—to whom isoniazid or deoxypyridoxine were given in increasing quantities until the tryptophan metabolism became abnormal—was different from that observed in patients with porphyria or scleroderma.[7,31] Patients to whom isoniazid was administered excreted predominantly hydroxykynurenine with smaller amounts of kynurenine and acetylkynurenine. Other metabolites of tryptophan were not excreted by patients in abnormally large quantities.

When deoxypyridoxine was administered, hydroxykynurenine was also the chief urinary metabolite of the amino acid, but increased quantities of kynurenine, acetylkynurenine, kynurenic acid, and, often, xanthurenic acid were observed.[31] In contrast, the majority of patients with scleroderma or porphyria excrete kynurenine as the chief urinary metabolite of the amino acid. The subjects with no known disease appear to excrete more hydroxykynurenine than kynurenine following the administration of a loading dose of tryptophan. Apparently, in scleroderma and porphyria, there may be some inability to hydroxylate kynurenine at a normal rate and in scleroderma, at least, this has not been overcome by the administration of large quantities of niacin,[7] which is a part of the cofactor for kynurenine hydroxylase.[16]

The interrelationships of minerals in nutrition and disease are an extraordinarily complicated subject.[32] Therefore, at this time, the

exact nature of the disturbance of metal ion balance in either scleroderma or porphyria cannot be indicated. Furthermore, there is no obvious reason why an imbalance in polyvalent ions develops in either condition. In both scleroderma and porphyria, the administration of chelating agents was associated with a diuresis of zinc and often of copper. Since the urinary excretion of zinc often fell to normal, or at least considerably reduced levels during the course of chelation, apparently administration of EDTA caused a negative zinc balance rather than increased absorption from the gastrointestinal tract.

The possibility that the symptoms of porphyria could be related to an imbalance of polyvalent cations in the tissues gains some support from the fact that the symptomatology of lead poisoning closely resembles that of porphyria.[1,3,33,34] Furthermore, in both porphyria and plumbism, abnormal quantities of porphyrins[35] and of δ-aminolevulinic acid[36,37] apparently exist in the urine. Both porphyria and plumbism appear to respond clinically to chelating agents,[1–5,38,39] which is another point of similarity. Since administration of various porphyrins or δ-aminolevulinic acid does not appear capable of reproducing symptoms of acute intermittent porphyria,[36,40,41] we suggest that manifestations of the disease might be the result of polyvalent cation imbalance. However, the mechanism by which this metal ion imbalance might develop in porphyria and the exact nature of the metal ion imbalance remain conjectural.[1,3]

Banerjee and Agarwal[42] studied the metabolism of tryptophan in patients with schizophrenia and found the urinary excretion of indole acetic acid increased in both normal and schizophrenic subjects after administration of tryptophan. Tryptophan administration, however, gave rise to increased urinary excretion of 5-hydroxyindole acetic acid in schizophrenic patients. No significant rise was detected in normal subjects. However, Zeller, Bernsohn, Inskip, and Lauer[43] administered tryptophan to schizophrenic patients and found no increase in the excretion of 5-hydroxyindole acetic acid in the urine, while, in the nonpsychotic group, 5-hydroxyindole acetic acid concentration rose significantly. Thus, opposite results were obtained in these 2 studies on the excretion of 5-hydroxyindole acetic acid by schizophrenic subjects.

It is difficult to compare the present studies with those of Banerjee and Agarwal.[42] In the first place, they used DL-tryptophan which has been found to be metabolized very differently from L-tryptophan.[44] Furthermore, the method used by Banerjee and Agarwal[42,45] failed to reveal kynurenine in the urine of normal human subjects and in the urine of patients with schizophrenia before or after the administration of tryptophan. The method used for the determination of kynurenine in these laboratories indicates that this tryptophan metabolite is present in all samples of human urine, normal or abnormal, and about one-third of the patients with schizophrenia studied here excreted abnormally increased levels of this metabolite following the administration of L-tryptophan. It is not surprising, however, that kynurenine could not be detected in normal human urine by the paper chromatographic method used by Banerjee and Agarwal, since studies in these laboratories indicate that normal levels of this metabolite can be seen on paper chromatograms of human urine only if the urine has been partially purified by column chromatography.

Of the 19 patients with schizophrenia who were used in the present investigation, 13 excreted normal or less than the expected amount of tryptophan metabolites in the urine. In no other group of human subjects studied to date have such low quantities of tryptophan metabolites been excreted by subjects following the ingestion of the standard 2 gm. dose of the amino acid. The response to tryptophan ingestion by some of the schizophrenic patients was so low as to make one suspect that they did not receive the supplement. Data from 4 patients were discarded for this reason, but it cannot be stated with certainty that these subjects failed to receive the supplement.

These studies, as well as those on patients with scleroderma, demonstrate the advisability of utilizing more than 1 metabolite of tryptophan to search for evidence for abnormal metabolism of the amino acid. The urinary excretion of xanthurenic acid has often been recommended as a means to detect abnormal tryptophan metabolism in various spe-

cies of animals. However, patients with porphyria or scleroderma may excrete from 8 to 10 times the normal quantity of kynurenic acid following a 2 gm. dose of tryptophan while the excretion of xanthurenic acid remains normal. Furthermore, patients ingesting isoniazid may excrete essentially normal quantities of xanthurenic acid while the urinary excretion of 3-hydroxykynurenine may be 20 to 40 times the expected level for a normal subject. The simultaneous determination of several metabolites along the same pathway also offers an opportunity to determine the sites of enzymatic block to a greater extent than would be possible when only 1 metabolite has been determined.

The partial or complete restoration of normal tryptophan metabolism associated with administration of chelating agents to patients with porphyria offers biochemical support for the clinical observation of the effectiveness of this form of therapy in porphyria.

Several of the urinary metabolites of tryptophan are excellent chelating agents. This is especially true of the 2-carboxy- and 8-hydroxyquinoline derivatives which include quinaldic acid, kynurenic acid, xanthurenic acid, xanthurenic acid 8-methyl ether, and 8-hydroxyquinaldic acid, all of which have been found in mammalian urine.[46–48] In the presence of a functional deficiency of pyridoxine resulting from an imbalance of polyvalent cations, as discussed above, the production of these metabolites from tryptophan may increase. The increased production of these metabolites might provide the patient with additional quantities of natural chelating agents which could then aid in the restoration of a normal balance of polyvalent cations. Thus, the production of these metabolites might provide a self-regulating mechanism for maintaining a normal balance of polyvalent cations. The administration of chelating agents such as EDTA or BAL may merely supplement the action of a natural system of chelating agents when the natural system has been overwhelmed in diseases such as porphyria and scleroderma. Studies to test this hypothesis are in progress.

SUMMARY

The urinary excretion of 9 metabolites of the essential amino acid L-tryptophan has been determined in 18 patients with acute, chronic, or mixed hepatic porphyria, 19 patients with schizophrenia, 8 patients with a variety of psychoses, and 10 patients with a variety of neurologic diseases. Of 18 patients with porphyria, 13 showed evidence of abnormal tryptophan metabolism characterized by increased urinary excretion of kynurenine, acetylkynurenine, kynurenic acid, hydroxykynurenine, and, occasionally, xanthurenic acid or other metabolites. A similar metabolic response was found in 6 of the patients with a variety of types of psychoses. Each of the patients with neurologic conditions metabolized tryptophan in an essentially normal manner.

Although the type of abnormality of the tryptophan metabolism of these patients suggests a functional pyridoxine deficiency, neither biochemical nor clinical improvement resulted following pyridoxine supplementation. Both clinical and biochemical improvement were often observed following treatment with chelating agents.

The possibility that the clinical and biochemical manifestations of porphyria might be related to a disturbance in polyvalent cation balance was discussed.

ACKNOWLEDGMENT

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The effects of lysergic acid after cerebral ablation

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LYSERGIC ACID DISTURBS the normal chimpanzee. Soon after ingestion of the drug, this animal becomes fearful and falls prey to severe perceptual aberrations.[1] This dramatic reaction is reminiscent of those described in some human subjects by various observers.[2–5] However, the reaction differs markedly from reactions of the monkey[6] and other experimental animals that have been administered the drug.[7]

Lysergic acid does not disturb the chimpanzee whose temporal lobes have been removed.[1] Indeed, after recovery from bitemporal lobectomy, the young chimpanzee can tolerate high doses without evidence of disturbance.

As reported here, lysergic acid has been given to chimpanzees whose frontal or temporal lobes have been removed. The reactions of these operated animals have been compared to those of normal contemporaries. All these reactions are reported after a consideration of the effects of frontal or temporal lobectomy.

MATERIALS AND METHODS

In these experiments, 15 healthy young chimpanzees were observed—7 females and 8 males. Average age of the animals is 7 years.

Each animal was observed for at least one year before these experiments. During that period, he was conditioned to handling and hand-feeding, as well as to close observation. Thus, observers and animals came to know each other. Similarly, after an animal came from operation, he was closely observed during the months which preceded administration of lysergic acid.

Each operation consisted of a unilateral lobectomy by subpial dissection under general anesthesia. In some animals, the temporal lobes were excised posteriorly to the petrous pyramid and mesially to the brain stem.[8] In others, the frontal lobes were removed to the margins of the sphenoid wings. In 1 animal, the uncus, amygdala, and pes hippocampus were removed on each side, as described by Scoville.[9] In another. the excisions were limited to the lateral temporal cortex and part of the underlying tapetum.

Eventually, through combination of unilateral procedures, 7 bilateral preparations were available. Of the 7, 4 had bitemporal lobectomies; 1, bifrontal ablation; 1, bilateral lateral temporal cortical ablation; and 1, bilateral ablation of the mesial temporal structures.

Since each preparation was at first unilateral, each animal received the drug after unilateral and bilateral ablations, as well as before operation.

The methods and circumstances of drug preparation and administration were similar or identical in all experiments. Lysergic acid was obtained from Sandoz Laboratories in powder or liquid form. The 20 γ per 1,000 cc. of powder was dissolved in distilled water and acidified with 1% aqueous tartaric acid. In either form, the drug was given orally after solution in a familiar liquid, such as Coca Cola or orange juice. Usually the chimpanzee drank this mixture when it was offered. However, some became wary of fluid offerings in the last experiments. In any event, the animal received the drug from the hands of a familiar person while in a familiar situation. The average dose was 60 γ per kilogram of body weight.

OBSERVATIONS

On the consequences of frontal lobectomy: Subject, Queenie, weight 15.8 kilograms.

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Read by title at the tenth annual meeting of the American Academy of Neurology, Philadelphia, April 21-26, 1958.

1) Right unilateral ablation: No obvious changes occurred.

2) Bilateral frontal ablation: After the second operation, individual and social changes occurred. The animal became unkempt and did not groom herself. She fed with either hand in a random manner. Her face was expressionless, and her extremities were hypotonic. Yet, she became hyperkinetic and spent most of her waking hours moving aimlessly about the run. Her movements were quick, jerky, and irrelevant to the environment. Socially, Queenie was rejected and lost her place in the hierarchy. Moreover, her peers attacked her frequently and without obvious provocation. Usually she responded to these attacks with an ineffectual defense and violent screams. Only the younger animals would tolerate her, but she did not assume any place in their hierarchy. She was isolated, restless, and indifferent to feeding, play, and handling. Nonetheless, she was tractable and mild when handled. Despite this tameness, she could not be trained for tasks or tests. Her neurologic examination was negative save for flattened facies and a slight, generalized hypotonia.

On the consequences of temporal lobectomy: Subject, Beebie, weight 14.5 kilograms.

1) Left unilateral temporal lobectomy: No obvious effect was seen.

2) Bilateral temporal lobectomy: No complications occurred after operation. For four weeks after the second operation, she did not seem to recognize familiar observers, runmates, or favorite foods. She was not blind. She would permit passive movement of her upper extremities and would hold the posture established by the movement. In all respects, Beebie was quite tame and easy to handle. After operation, any observer could handle her, while before, only 1, or perhaps 2, were able to do so. In the first four weeks after the last operation, her neurologic examination was negative. She also lost her tendency to maintain postures after passive movement. Then, in the succeeding two months, she resumed her preoperative activity rates, play habits, and position in the hierarchy. A year after the last operation, she vocalizes normally; her play, feeding, and sexual habits and her social relationships are indistinguishable from those of her peers. She is somewhat more tame. However, no evidence is seen of abnormal oral habits or visual agnosia. According to crude tests, her visual fields are full and no evidence exists for visual deficits. She can solve simple problems—indeed, she learns to remove an orange from a closed and fastened box after a three-minute demonstration. Immediately after such demonstration, she has repeatedly extricated the orange successfully. However, she cannot do this if demonstration and task are separated by ten minutes' distraction. However, her normal peers succeed in the task, despite ten minutes' interruption between learning and doing.

On the consequences of bilateral removal of mesial temporal structures: Subject, Hazel, weight 13.5 kilograms.

1) Right unilateral mesial temporal ablation: No obvious effect was seen.

2) Bilateral—left after right—mesial ablation: This animal was mute and would permit passive manipulation of the extremities for one month after the last operation. During those four weeks, she would maintain a posture developed by passive movement for as long as five minutes. She did not seem to recognize favorite handlers and was easy to handle. Before operation, she had been difficult. Actually, even strangers could take her out of the cage. Left to herself, Hazel was relatively inactive and her feeding was indifferent. She spent most waking hours staring at the wall. However, in the second postoperative month, she resumed her previous habits and activities. Thereafter, she was not markedly different from her normal contemporaries. Her neurologic examination was negative.

On the consequences of bilateral ablation of the lateral temporal structures: Subject, Abel, weight 20 kilograms.

1) Bilateral excision of the lateral temporal cortex and underlying white matter did not produce any obvious changes in this animal.

On the reaction to lysergic acid after bifrontal or bitemporal lobectomy. Subjects, Queenie (see above), bifrontal ablation (Fig. 1), and Beebie (see above), bitemporal ablation (Fig. 2).

Each animal received 600 γ of lysergic acid orally at approximately 11 A.M. on August 11, 1958. Their reactions were observed as they sat or moved about in the same run. For thir-

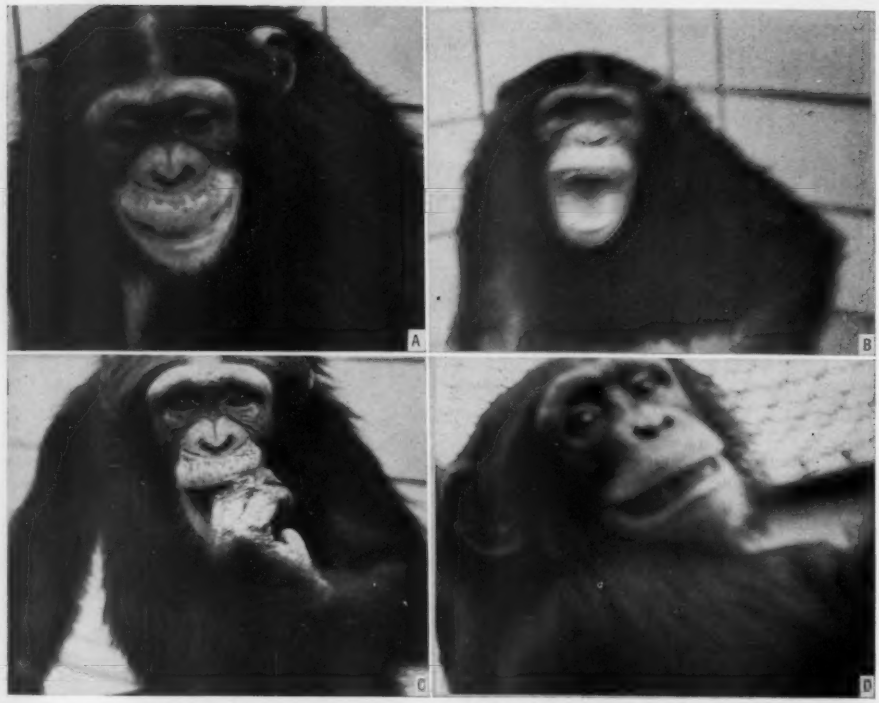

Fig. 1. The effects of lysergic acid after bifrontal lobectomy in Queenie. (A) Grimace, scream, and piloerection. (B) Charging the observer. (C) Chewing her left hand. Pupils dilated, piloerection. (D) Screaming and jumping.

ty minutes after ingestion of the drug, no changes were noted in either animal. During this time, Queenie was moving restlessly about the run while Beebie played with one of the observers. Then Beebie began to play with a feeding pan in the corner. Suddenly Queenie screamed, defecated, and jumped in the air. As she jumped, she continued to scream and began to beat the air above her head with her right hand. She salivated, and her hair stood on end as her pupils dilated—despite high intensity illumination (Fig. 1A). Next, she charged the observer who was taking her picture (Fig. 1B). Her teeth were bared, and her hands were grasping for him. He dodged away, and she stopped quickly. Then she began to chew her left hand vigorously (Fig. 1C). All this time, Beebie was quietly eating an orange (Fig. 2A).

Once more Queenie screamed and struck at the air before her face with her left hand. As before, she charged the nearest observer but this time missed him completely. She fell against the wall and began to whimper and bark as she covered her head with both hands. Thereafter, she continued a frenzied round of rapid running, jumping, and screaming (Fig. 1D). Intermittently, she stared quickly above her head—pupils dilated, hair on end, hyperventilating. She did not respond to food, voice, or gesture and fought off, with vicious slashing of teeth and hands, any attempts at restraint. Noise and flashing lights seemed to increase the disturbance. In the meantime, Beebie ate another orange, played with a pan, solved a box problem, and responded to voice, gesture, pain, noise, and light in a normal fashion (Figs. 2B and C). She did try to

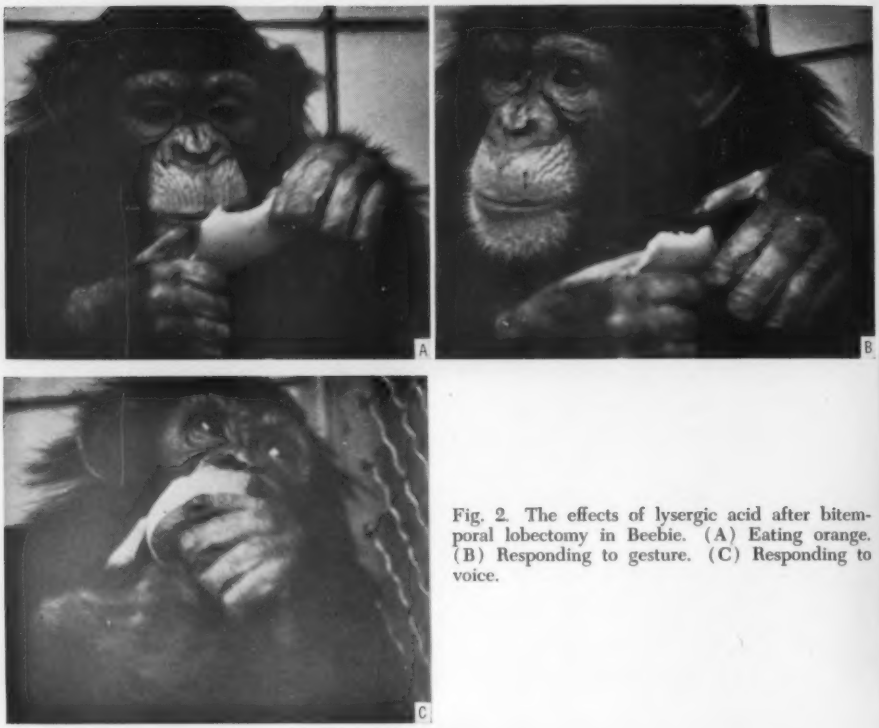

Fig. 2. The effects of lysergic acid after bitemporal lobectomy in Beebie. (A) Eating orange. (B) Responding to gesture. (C) Responding to voice.

avoid Queenie's mad antics, but she did not seem alarmed by them.

Queenie's antics continued for two hours. Finally, she seemed oblivious to her surroundings. Her screams subsided, and her restless movements were interrupted by periods of sitting and staring. In one such episode, she seemed to fall asleep. Her head fell on her chest, and she jerked erect with quick movements of head, neck, and trunk. Then she walked about with an ataxic gait and staggered to the right. This activity was abruptly interrupted by another episode of unresponsive staring. These periods of absence became more frequent and more abrupt in onset, until one followed another at intervals of approximately three minutes. As she stopped and stared, she was unresponsive to noise, light, touch, pressure, and pain. Each episode lasted approximately five seconds. Shortly thereafter, she fell to the ground and lay in a frog-like position. Her breathing was stertorous and she did not respond to various stimuli. This coma lasted for thirty minutes. Over a period of two hours, she gradually recovered.

On the reactions to lysergic acid after mesial temporal or lateral temporal ablations. Subjects, Hazel, bilateral mesial temporal ablation, and Abel, bilateral lateral temporal ablation.

Each animal received 600 γ of lysergic acid by mouth. For thirty minutes, neither seemed affected. Then Hazel screamed and pointed at the air before her. She screamed again, covered her eyes, and ran backward across the run. There she sat and whimpered. Her hands were held tightly across her eyes. Suddenly she jerked them from her face and looked at the air above. She screamed, defecated, and began to salivate. Piloerection and pupillary dilation occurred. After screaming, she ran cowering to the other side of the run.

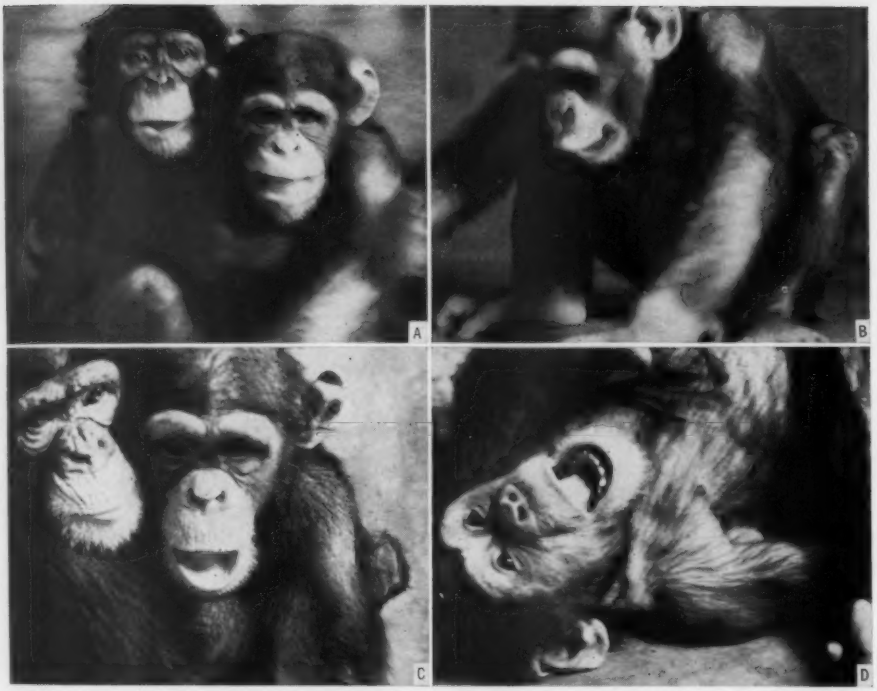

Fig. 3. The effects of lysergic acid after bitemporal lobectomy in Beebie compared to its effects on the normal chimpanzee, Sampson. (A) (Beebie on left, Sampson on right.) Sampson is salivating and grimacing. His labial folds are flattened. Beebie appears normal as she holds him. (B) Sampson screaming as he beats the floor. Piloerection is seen. (C) Sampson (right) has flattened facies, and he is hyperventilating. Beebie (left) holds him in a protective grasp. (D) Sampson screams as he lies on his back and kicks or strikes at the air above him. Note piloerection.

These activities continued for approximately two hours.

During this time, Abel ate oranges, played with a water faucet, and did some gymnastics. He responded to voice, gesture, food, and playthings. His pupils were dilated, and his skin seemed very warm. He had some salivation.

On the comparison of the reactions of a normal and a temporal lobectomized chimpanzee. Subjects, Sampson, weight 20 kilograms, normal condition, and Beebie, bitemporal ablations including mesial structures.

Each animal received 600 γ of the drug by mouth at 10 A.M. and played together in the run for approximately thirty minutes. Suddenly, Sampson, the normal animal, stopped his play. His pupils dilated. He seemed to stare, and his mouth opened in a grimace as he began to salivate (Fig. 3A). His face flattened, and he began to hyperventilate. Then his hair stood on end, and he screamed and leaped backward. As he moved, he struck at the air before him with both hands (Fig. 3B). When he landed, Beebie moved to his side and hugged him with her right arm. She looked directly at the photographer as she did this (Fig. 3C). Sampson broke away from her grasp and screamed. He began to run about while he alternately screamed and whimpered. Once Beebie tried to stop him, but he pushed past and beat at the air behind her. She ignored him and began to play with a pan in the corner. In the meantime, his violent move-

ments, shrill screams, and deep whimpers continued. He salivated and the piloerection continued. Occasionally, he interrupted his pacing while he struck at the air above his head. As he resumed, he seemed oblivious of Beebie and the observers. Gradually, over a two-hour period, he became disoriented and attempted to crawl on his back (Fig. 3D). Then his gait became ataxic, and he fell into a frog-like position. He slept for approximately ten minutes and then began a recovery which lasted about eight hours. Beebie remained unchanged.

DISCUSSION AND SUMMARY

The observations reported above are typical of 70 experiments conducted over a two-year period. In these tests, all animals were used in various combinations. According to these observations, the young chimpanzee reacts to lysergic acid with a panorama of abnormal behavior which is consistent and characteristic. If such an animal is subjected to bifrontal lobectomy, his reactions in ordinary situations are radically changed; yet his reactions to the drug are not. Paradoxically, he reacts to lysergic acid in the same way as before operation, although this massive ablation has obviously affected all other reactions in social, test, and training situations. Indeed, among his various postoperative responses, only the drug reaction remains comparable to those observed before bifrontal lobectomy. Apparently, intact frontal lobes are not essential for the characteristic drug reaction.

On the other hand, if such an animal is subjected to bilateral temporal lobectomy, his responses to ordinary situations are remarkably unchanged, except for a four-week period after surgery. Yet, his response to the drug is obviously changed. Some autonomic reactions remain thereafter, but panic or perceptual aberration does not increase in the postoperative drug reaction. However, unilateral temporal lobectomy does not change the animal's reaction to lysergic acid. Nor does lobectomy alter social or training responses. Apparently, one or the other temporal lobe is essential for this drug reaction in young chimpanzees.

When the temporal ablation includes only the mesial structures, the reaction to lysergic acid is unchanged. Yet, after selective ablation of both lateral temporal cortices, the reaction changes or disappears. Perhaps the lateral temporal cortex and its tapetal connections form essential links in the neurologic chain which constitutes the background of this panoramic reaction.

The reaction itself is a compound of perceptual aberration and panic. As the animal reacts, he may look at his hand and scream. Then his pupils dilate, and his hair stands on end. Or he will react abnormally to the usual forms, colors, and sounds of his habitual surroundings.

According to recent reports, the lateral temporal cortex is concerned with perception.[10] The human[11] reaction and the reaction of the chimpanzee to administration of lysergic acid are certainly characterized by gross perceptual disturbances. Removal of the lateral temporal cortices prevents this gross perceptual aberration in the chimpanzee. Perhaps the drug disturbs perceptual mechanisms represented in the gray mantle of the temporal lobe.

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Progressive muscular weakness and pain as symptoms of adult Fanconi syndrome

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THE COMBINATION OF progressive pain in the lower back and in the legs, abnormal gait, and weakness suggests the presence of a primary neurologic disease.

These symptoms are often the presenting complaints in adults with Fanconi syndrome, a metabolic disorder. Not infrequently, patients with this syndrome are seen by the neurologist in the early stages of the condition and the underlying disorder is not recognized.

The Fanconi syndrome is a somewhat variable complex of metabolic errors resulting from defective renal tubule reabsorptive mechanisms. This defective tubular function results in renal glycosuria, renal phosphaturia, renal aminoaciduria, and, at times, excessive renal loss of other substances.[1,2] Systemic hyperchloremic acidosis often occurs. The Fanconi syndrome is recognized most commonly in children, in whom it is associated with stunted growth, rickets, and acidosis. In children, death usually occurs before puberty.[3]

Less generally recognized is the fact that the syndrome may occur in adults and in persons who previously appeared to be in good health.[4] In adults, metabolic errors are usually less severe and the disease, even when untreated, follows a more chronic course.[2] Osteomalacia is a feature of the syndrome in the adult, and the major symptoms are those of osteomalacia. The previously reported cases of adult patients with Fanconi syndrome were recently summarized.[4] We are reporting a case in which the presenting complaints were those of weakness in the lower extremities, waddling gait, and pain in the lower back and in the legs.

CASE REPORT

A 67-year-old woman came to the Mayo Clinic in December 1957 because of progressive weakness in both legs and pain in the back and left leg of two years' duration. An intermittent sensation of painful grabbing had also developed in her left thigh two years before. About one year prior to admission, she gradually developed a shuffling, unsteady gait.

The patient noticed that on rising from a sitting position she could not immediately walk and attributed this to a painful feeling of tightness in her hips.

She began having brief, sharp pains "like a flash of lightning" in the left thigh and in the lower back four months before admission. These pains usually occurred when she rose from a sitting or lying position. Similar sharp pains began two months before admission which extended around the right thoracic wall from the epigastrium to the midthoracic portion of the spinal column. Movements such as walking, stooping, or jolting seemed to precipitate them. She was essentially free of pain when recumbent. Dull, aching pains were noticed in multiple places at various times. Her general health had remained good, and her only other complaint was that of moderate fatigue.

Sugar had been found in the urine for the first time six years prior to her admission, and sugar had been present on each subsequent determination. The concentration of blood glucose after fasting was repeatedly normal. Albuminuria had been known to be present for two years. Her urine had not contained sugar or albumin ten years before. Her past history and her family history were not remarkable.

At physical examination, the patient was of normal proportions and did not look ill. Her blood pressure was 124 mm. of mercury systolic and 84 mm., diastolic. She walked with a hesitant, waddling gait. The patient had a full range of motion in the hips and back, although she moved guardedly because sudden movement might set off severe pains in the back and legs. The anterior margins of the ribs were tender to pressure, and tenderness occurred over the vertebral spinous processes. Careful muscle testing revealed no objective muscle weakness. Deep tendon reflexes were slightly increased, and the left plantar response was questionably extensor. The remainder

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of the physical and the neurologic examinations gave negative results.

The concentration of hemoglobin was 13.7 gm. per 100 cc. of blood and the leukocyte count was 4,800 per cubic millimeter, with a normal differential count. Repeated urinalyses showed a specific gravity that ranged from 1.009 to 1.020; alkaline reaction; albuminuria, grade 2; glycosuria, grade 1 to grade 4, with Benedict's solution and with a sugar enzyme test for glucose; occasional traces of acetone; and occasional pus cells. Serologic reactions for syphilis were negative. The sedimentation rate was 10 mm. (Westergren method). Other values were: blood urea, 36 to 51 mg. per 100 cc.; serum sodium, 128 mEq. per liter; serum potassium, 3.6 mEq. per liter; serum chloride, 111.3 mEq. per liter; serum bicarbonate, 17.9 mEq. per liter; serum calcium, 9.8 mg. per 100 cc.; serum phosphate, 2.0 mg. per 100 cc.; and serum alkaline phosphatase, 21.9 King and Armstrong units. Electrophoretic analysis of the serum protein by filter-paper method gave the following values per 100 cc.: albumin, 3.60 gm.; alpha-1 globulin, 0.34 gm.; alpha-2 globulin, 0.76 gm.; beta globulin, 1.10 gm.; and gamma globulin, 1.25 gm. Total serum protein measured 7.05 gm. per 100 cc. A glucose tolerance test gave the following concentrations of glucose per 100 cc. of blood: 95 mg. after fasting; 188 mg. after one hour; 155 mg. after two hours; and 91 mg. after three hours. When the glucose tolerance test was repeated after two days of high-carbohydrate intake, the two-hour value for glucose was 119 mg. Glucose was present in all urine specimens.

Examination of aspirated sternal marrow showed normal cellularity with focal areas of eosinophilia and a diffuse increase in lymphocytes. No evidence was found of multiple myeloma. Roentgenographic examination revealed demineralization and mild hypertrophic changes in the cervical, thoracic, and lumbar portions of the spinal column and demineralization of the pelvis. Pseudofractures, that is, bandlike radiolucent zones of decalcification extending from the cortex across the long axis of the bone, were present on the inferior aspect of the neck of the left femur, the inferior ramus of the right pubic bone, and the seventh rib posteriorly on the right. Some demineralization occurred in the skull and mandible, but the lamina dura was normal. No bone lesions were found which suggested multiple myeloma.

Myelographic examination of the entire spinal canal showed no evidence of abnormality. The spinal fluid contained 90 mg. of protein per 100 cc. and 1 lymphocyte per cubic millimeter; the pressure was normal. Electromyographic studies gave negative results except for minimal fibrillation potentials in the left paraspinal muscles at the level of the third lumbar spinous process.

The urine contained protein showing the heat-precipitable and heat-dissolvable characteristics of Bence Jones protein. The concentration of total protein in the urine was 450 mg. per 100 cc. Electrophoretic separation showed the greater part of the urinary protein to be a glycoprotein with a motility similar to that of the alpha-2 glycoprotein of serum. The twenty-four-hour urinary excretion was: 927 mg. for amino nitrogen; 5,966 mg. for total nitrogen; 11.6 gm. for sugar; 362 mg. for calcium; 714 mg. for phosphorus; and 39.4 mEq. for ammonia. The twenty-four-hour titratable acidity was 37.2 mEq.

The symptoms changed little during a three-week period of study and observation prior to the beginning of treatment. Therapy was started with daily oral administration of 250,000 units of vitamin D and 45 mEq. of potassium. After one week, her serum potassium had increased to 4.1 mEq. per liter from 3.6 mEq. and her serum phosphate to 2.7 mg. per 100 cc. from 2.0 mg. The pain changed little during the first few weeks of treatment. After four weeks, the patient reported marked improvement and was able to discard her cane. She reported no pain, normal gait, and general good health eight months after starting treatment.

COMMENT

The clinical symptoms in this case, as in others of the adult Fanconi syndrome, included those of muscular weakness, disturbance in gait, and skeletal pain. These symptoms are predominantly due to the osteomalacia, and similar symptoms result from osteomalacia from other causes.[5] Although the urine contained an abnormal protein which showed the solubility characteristics of Bence Jones protein, no other evidence suggested a diagnosis of multiple myeloma; such a protein is known to occur in conditions other than multiple myeloma. The etiology of the basic renal disorder was not apparent.

Weakness was a major complaint in this case, although, on careful muscle testing, no objective evidence of actual muscle weakness was found. Similarly, the electromyogram revealed no evidence of denervation. The feeling of weakness, therefore, seemed to be due to reluctance to forcibly contract the muscles at painful sites, with resulting splinting of the affected extremity. It is suspected that many of the references to weakness in other cases are based on the patient's subjective complaint of weakness rather than on objective findings of weakness on muscle testing. In patients with long-continued illness and with painful bony lesions of osteomalacia, atrophy may occur secondary to disuse in the involved musculature. Low levels of serum potassium are

common in the Fanconi syndrome and may account for episodes of severe weakness and collapse.[1]

Gait becomes hesitant, slow, and awkward and assumes characteristics of waddling such as is seen with weakness about the hip girdle. A transient sensation of hesitancy or of insecurity is commonly noticed on standing and on attempting to start walking. The prominence of this symptom was such as to cause consideration of a diagnosis of myotonic dystrophy in Milkman's original case.[6]

Pain is the most common symptom.[4] The onset of pain is usually slow and insidious, and different parts of the skeleton may be progressively involved. The pain may be dull and constant or sharp and cramplike.[4] This patient's description of pain as "like a flash of lightning" was suggestive of tabetic pain. This pain may have been secondary to pseudofractures or to involvement of the spinal nerve roots. The most common sites of pain are the hip, thigh, and lower back. Often first noticed on arising from a supine or sitting position, pain is aggravated by motion and minimal or absent when the patient is lying quietly. With progression of the disease, pain tends to become more severe and more extensive. In some instances, osteomalacia may result in compression fractures of the spinal column with ensuing compression of the spinal cord.[7]

The neurologic symptomatology of the adult Fanconi syndrome is similar to that seen in other conditions causing osteomalacia. Vicale[8] discussed these symptoms as those of a muscular syndrome and referred to the condition as an amyotrophic lateral sclerosis-like syndrome. In our experience, the predominance of pain among these symptoms very frequently suggests spinal-cord tumor, metastatic carcinoma, or protruded intervertebral disk. Early, the illness may be difficult to differentiate from a psychogenic conversion reaction. Objective findings in the early stages are minimal and often out of proportion to the intensity of the symptoms.[9]

Treatment is generally successful in relieving the symptoms of pain, weakness, and abnormal gait.[1,10,11] Therapy is aimed at control of osteomalacia, hypokalemia, and systemic acidosis. Massive doses of vitamin D in the range of 200,000 units or more daily are necessary to counteract the metabolic defects that are producing osteomalacia. With adequate treatment, relief of the skeletal pains can be expected over a period of weeks, and the pseudofractures generally recalcify and heal over a longer period.[7,11,12] Potassium and alkali are given in doses adequate to control the hypokalemia and acidosis. Since no curative measures exist for the basic renal tubular defect, treatment must be continued indefinitely.

Early diagnosis is highly important, because treatment is generally successful in controlling and reversing changes due to osteomalacia. If treatment is not given, progressive incapacitation and debility occur, with ultimate development of pseudofractures, pathologic fractures, and deformities. Because of the predominance of the symptoms of muscular weakness with pain, the neurologist will frequently have the opportunity to suspect the underlying condition and to direct investigation along lines leading to the diagnosis.

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Early surgical treatment of aneurysms of the circle of Willis

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NUMEROUS AUTHORS[1–4] have reported on the high number of deaths in the first weeks after the rupture of an intracranial aneurysm. A recent report[5] calls attention to the fact that "if those patients who terminate fatally in the early danger period are excluded, conservatively treated aneurysms and surgically treated aneurysms have nearly the same prognosis."

One might conclude from this that operation is of limited value in the treatment of intracranial aneurysms. Whether this is so for the individual who has survived the initial hemorrhagic episode is as yet not known; sufficient data are not available to enable sweeping conclusions to be drawn about the long-term aspects of intracranial aneurysms. However, it seems unwise to assume that surgical intervention is of little or no benefit in the immediate postrupture period. In fact, we feel that major therapeutic efforts should be directed to this phase of the illness if any significant benefits are to accrue in the treatment of aneurysms. We also feel that the best long-term results can be expected when an aneurysm has been successfully and completely obliterated by direct intracranial surgery. The following preliminary report concerns 46 patients who have had intracranial clipping of an aneurysm in the so-called early danger period following rupture.

In order to provide comparative data, patients were grouped in a manner similar to the criteria employed by Botterell.[6] Patients were subdivided according to age, site of aneurysm, length of time after bleeding, and neurologic condition. Only by such grouping can we arrive at a meaningful assessment of the various types of aneurysm therapy. It is hoped that future reports will accept these criteria to facilitate pooling of data and statistical analysis.

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CASE MATERIAL

Of the 46 patients, all but 3 had documented evidence of recent subarachnoid hemorrhage. These 3 were operated on the day that their aneurysm developed acute signs — sudden onset of intense retroorbital pain with ipsilateral extraocular muscle paresis or the like. Bilateral carotid angiography was carried out in all patients. As soon as the diagnosis was confirmed, operation was performed. All were operated on within two months of their presenting signs.

We find in reviewing our group of 46* patients that 11 (see table, B, C, and D) were either comatose, moribund, or over 55 years of age. As can be seen from this chart, the results were so unsatisfactory after early operation in these groups that we have now been led to avoid intracranial operation for most patients in these categories.

On the other hand, our retrospective analysis of patients over the past few years indicates that patients under 55 years old who are not comatose will, as a rule, readily tolerate early intracranial operation. To counterbalance this selectivity, we have *not* excluded patients with vascular hypertension, multiple aneurysms, active subarachnoid hemorrhage, or presumed technical difficulties in a direct attack on their lesion.

Turning to the 35 patients less than 55 years old and not comatose at the time of surgery,

*This represents the personal series of 2 of us (J.L.P. and J.R.).

TABLE 1
RESULTS OF DIRECT INTRACRANIAL ATTACK ON 46 RUPTURED ANEURYSMS OF THE CIRCLE OF WILLIS

	Operation day after hemorrhage	Sex	Age	Location				Multiple aneurysms	Method of operation			Remarks	Result
				IC	MC	AC	ACC		N	H	TC		
GROUP A: Under 55 years: not comatose													
0 to 7 days													
H.T.	1	F	40	X				X		X		IC aneurysm on opposite side also	XX
N.S.	1	F	34	X						X	X	Confused and restless preoperatively. Aneurysm bleeding at operation	D
H.S.	3	F	53	X						X			XX
H.M.	3	F	43	X						X			XX
B.K.	3	F	54	X						X		Myocardial disease; blood pressure, 210/120 preoperatively. Good recovery	XX
F.R.	6	M	31				X	X		X	X	Figs. 1 to 3. Two aneurysms on LMC also	XX
E.B.	7	F	54		X					X		Mild postoperative hemiparesis	XX
8 to 14 days													
H.N.	8	F	41		X					X	X		XX
G.V.	9	F	49	X						X	X		XX
L.E.	10	F	36				X			X	X	Working full-time; memory impaired	XX
N.M.	11	F	29				X		X			9-year follow-up.	XX
R.T.	12	M	31	X						X		Died of septicemia after good early postoperative recovery	D
A.D.	12	F	33				X			X	X	Fig. 4. Arm weak; normal gait; working	XX
J.H.	14	F	21	X						X	X	7 months pregnant at time of operation; Normal full-term infant	XX
J.W.	14	F	34	X						X	X		XX
C.L.	14	M	49	X						X		2-year follow-up. Aphasic and hemiparetic preoperatively; aphasia disabling postoperatively	O
15 to 21 days													
M.M.	16	F	37	X						X	X	Hemiparetic preoperatively; normal postoperatively	XX
V.J.	17	F	30	X						X		Residual aphasia; not disabling	XX
E.C.	17	F	46		X			X	X			Hemiplegic and aphasic preoperatively; paretic and dysphasic postoperatively; working full-time, 5 years	XX

KEY FOR TABLE 1. *Location:* IC = Internal carotid (including posterior communicating); MC = Middle cerebral; AC = Anterior cerebral; ACC = Anterior communicating. *Method of operation:* N = Normothermic anesthesia; H = hypothermic anesthesia; TC = Temporary clips used. *Results:* XX = Alive, well, working; O = Alive, but incapacitated; D = Dead.

TABLE 1—*(continued)*

	Operation day after hemorrhage	Sex	Age	Location				Multiple aneurysms	Method of operation			Remarks	Result
				IC	MC	AC	ACC		N	H	TC		
E.S.	17	M	47				X			X	X	Slow mentation; poor memory; not working	O
C.L.	18	F	46		X					X	X	Arm paralyzed; walks with brace; not working	O
Group A: Under 55 years: not comatose													
22 to 60 days													
I.B.	25	F	32	X				X		X		Fig. 5. 3 months pregnant at time of operation; normal full-term infant. Aneurysm opposite middle cerebral also obliterated later. No hemorrhage; two-year follow-up	XX
H.G.	25	M	44	X						X		3-year follow-up	XX
G.W.	30	F	42	X						X	X	Hemiparetic preoperatively; normal postoperatively	XX
J.P.	32	F	40	X						X			XX
M.C.	35	F	52				X		X				XX
M.R.	37	M	40	X						X		Slight residual aphasia; severe preoperatively	XX
C.M.	42	M	29	X						X		Aneurysm packed with muscle; discharged well· died in one month of postoperative recurrent hemorrhage	D
E.W.	42	F	47				X			X		2-year follow-up	XX
N.M.	42	M	40	X						X		Recovered from preoperative aphasia. 3-year follow-up	XX
L.S.	42	F	23	X						X		4-year follow-up	XX
L.R.	43	F	36				X			X	X	Right AC clipped; good condition first day; died of massive right cerebral edema	D
E.S.	49	M	30			X			X			Temporal AC artery bypass. 10-year follow-up	XX
T.H.	54	F	48	X						X		4-year follow-up	XX
T.H.	54	F	54				X					4-year follow-up	XX
Group B: Under 55 years: comatose													
Y.C.	2	M	40	X					X			Comatose preoperatively with intracerebral hematoma	D
M.W.	3	M	41	X					X			Comatose preoperatively	D
M.K.	11	M	47	X						X		Comatose preoperatively	D

TABLE 1—*(continued)*

	Operation day after hemorrhage	*Sex*	*Age*	*Location* IC	MC	AC	ACC	*Multiple aneurysms*	*Method of operation* N	H	TC	*Remarks*	*Result*
GROUP C: Over 55 years: not comatose													
E.K.	1	M	59				X			X	X	Aphasia appeared during angiography; mild aphasia postoperatively	O
R.B.	2	M	58				X			X	X	Well until sudden death four weeks postoperatively; recurrent hemorrhage; aneurysm, muscle wrapped	D
B.G.	3	F	58	X					X		X	Died one day postoperatively; coronary occlusion at autopsy	D
B.T.	4	F	57	X				X		X		Full immediate recovery; relapse after fall; no recurrent hemorrhage; 7 aneurysms	O
K.B.	7	F	56	X					X			Good preoperative condition; good first day postoperatively; died of massive softening fifth day	D
GROUP D: Over 55 years: comatose													
M.B.	2	F	67		X				X		X	Partial recovery first day; died two days postoperatively; tantalum clip open at autopsy; hypertensive	D
F.L.	4	F	58	X						X		Semicomatose; died of massive cerebral edema	D
C.D.	14	F	59	X					X			Semicomatose preoperatively; large intracerebral hematoma at operation	D

we find that 16 were operated on within two weeks of the onset of symptoms. Of the 35 patients, 4 died. The mortality rate, therefore, was 11%.

LOCATION OF THE ANEURYSMS

The location of the aneurysms in these 35 patients is indicated in Table 1: 21 arose from the internal carotid artery (IC), including 6 from the posterior communicating artery (PC); 4 from the middle cerebral artery (MC); 1 from the anterior cerebral artery (AC); and 9 from the anterior communicating artery (ACC).

We wish to call particular attention to the fact that 12 aneurysms involved the anterior cerebral system, notoriously subject to recurrent, fatal hemorrhage even though treated by carotid artery ligation in the neck.[7] The same principle applies, although to a lesser extent, to aneurysms of the middle cerebral artery.

It is only those aneurysms which originate from the internal carotid or adjacent posterior communicating arteries that can be expected to respond well to carotid ligation in the neck.[7–9] Aneurysms of the internal carotid, however, also represent the most favorable lesions for direct intracranial surgical attack; they are quite easily clipped and postoperative morbidity is low.

Fig. 1. (*Case F.R.*) Angiograms showing large aneurysm of anterior communicating (ACC) artery (*see case report*). (*Top*) Anteroposterior projection. (*Bottom*) Lateral projection

DIAGNOSTIC MEASURES

A complete physical and neurologic examination, x-rays of skull and chest, lumbar puncture, blood studies including clotting and bleeding times, urinalysis, and electrocardiography were carried out in all our patients, usually within two to three hours of their admission. Arteriographic studies consisting of bilateral carotid seriograms in both the anteroposterior and lateral projections were then done. In some patients, oblique seriograms were also necessary in order to establish the relationship of the aneurysm to its parent vessel.

SURGICAL TECHNIC

Direct intracranial operation was carried out in all 46 patients. In a few, the carotid arteries in the neck were first exposed in order to afford temporary control of this vessel, if necessary. However, in our later cases, we have used this maneuver infrequently. All but 10 of our early surgery cases were operated on under hypothermic anesthesia;[6] the body temperature was approximately 28° C. when the aneurysm was clipped. In 17 patients, temporary clips[10–12] were employed* to occlude the immediate proximal supply to the aneurysm, enabling us to dissect these lesions without the usual fear of rupture. In only 1 patient were we unable to place a clip across the aneurysm or its neck; we were forced to pack the lesion with muscle. This patient was discharged, apparently in good health, but died of a recurrent hemorrhage one month later.

CASE REPORT

The following case report illustrates some of the principles of early intracranial aneurysm surgery under consideration and includes a brief description of the temporary clip (TC) method[10–12] under hypothermia that has proved so helpful. This case report also indicates that intracranial surgery is not necessarily contraindicated, even though the patient may have multiple aneurysms.

A right-handed, 31-year-old mechanic was first admitted to another hospital because of sudden subarachnoid hemorrhage and rapid failure of vision in his left eye. A left, percutaneous, carotid angiogram showed 2 small saccular aneurysms arising from the left middle cerebral artery. Prompt occlusion of the left internal carotid artery with a Selverstone clamp was well tolerated. Vision in the left eye, however, did not improve.

A second severe subarachnoid hemorrhage occurred eight days later. Right carotid angiography showed a large saccular aneurysm of the anterior communicating artery with considerable local vasospasm and some displacement of the adjacent anterior cerebral arteries (Fig. 1).

On admission to the Neurological Institute of New York five days after the second hemorrhage, the patient was lethargic, had marked nuchal rigidity and left-sided hyperreflexia and was almost completely blind in the left eye. He was considered a Grade II patient.[6]

Intracranial operation was done early the next morning under hypothermia at 28° C. No significant cardiac irregularities occurred

*Kees Surgical Specialty Co., Alexandria, Ky.

during surgery,[13,14] thanks to the excellent precautions taken by the anesthesiologists under the direction of Dr. B. Raymond Fink.

Following our usual custom for this type of aneurysm, a bifrontal bone flap was turned (JLP) and the falx divided anteriorly so that both frontal lobes could then be separated and gently retracted. A temporary removable clip (TC), similar to a miniature bulldog clip, was placed on the right anterior cerebral artery, and another was placed on the left—as close to the anterior communicating artery as possible. It was then possible to dissect this large, multilobed, saddlebag type of aneurysm freely and boldly without fear of rupture. Small accessory arteries, such as so often enter this type of aneurysm, were permanently clipped off. The large irregular sac, virtually glued over, as well as under, the optic chiasm and left optic nerve, was then carefully dissected free and obliterated by permanent metal clips. The circulation of both anterior cerebral arteries was preserved intact.

Diagrams of the procedure prepared from color photographs at operation show the aneurysm before (Fig. 2A) and after its permanent clipping (Fig. 2B) and indicate how the temporary clips were used to reduce arterial pressure within the aneurysm during its dissection. The findings and procedure apply to 3 similar large anterior communicating aneurysms (E.S., A.D., and L.E.) so treated, and other smaller aneurysms in this location. In this patient, as in a number of others, it was also found helpful for adequate exposure to resect a small bit of brain tissue adjacent to the aneurysm.

The postoperative course was remarkably smooth except for a slow recovery from preoperative lethargy. Now, approximately one year later, the patient is his usual self, has improved vision in his left eye, and is engaged in full-time work at his former occupation (Fig. 3). A postoperative photograph of another patient who had a similar large aneurysm of the anterior communicating artery is shown in Figure 4. Postoperative angiography showed good filling of both her anterior cerebral arteries.

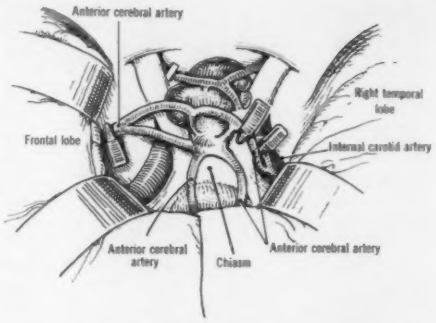

Fig. 2A. (*Case F.R.*) Diagram of operative findings prepared from color photograph. Note temporary clips in position on left anterior cerebral and 2 branches of abnormal right anterior cerebral artery.

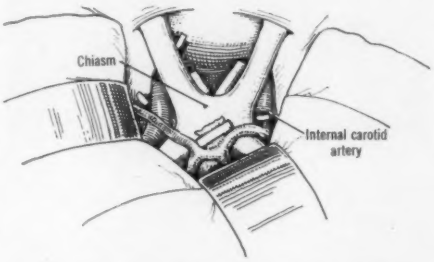

Fig. 2B. (*Case F.R.*) Diagram of operative findings prepared from color photograph after excision of aneurysm

COMMENT

This case illustrates several points concerning the management of bleeding intracranial aneurysms. First of all, bilateral angiography is clearly essential, since multiple aneurysms may be present, as in this patient. Furthermore, bilateral angiography may reveal important anomalies of the circle of Willis that may vitally influence the type of surgical intervention. It is significant in this patient, moreover, that no vasospasm was found near the 2 small aneurysms initially discovered on the left side. This should have been regarded, in the absence of cerebral arteriosclerosis, as a strong indication that the source of bleeding was elsewhere, for local cerebral vasospasm is frequently an excellent angiographic sign that indicates the site of bleeding.[15,16]

Intracranial operation in this patient was clearly indicated, since it would obviously have been impossible to ligate both the right

Fig. 3. (*Case F.R.*) Photograph five months after operation. The patient is working full-time at original occupation one year post-operatively (*see case report*).

as well as the left carotid arteries in the neck. Promptness in surgery was also indicated in view of the second serious hemorrhage eight days after initial bleeding. A third and probably fatal hemorrhage could otherwise be expected at any time, as hemorrhages are very apt to recur, as in this patient, approximately eight days after initial bleeding. Parenthetically, neurologic signs, such as hemiplegia, may also develop on the sixth to eighth day after initial bleeding—as seen in a number of our patients—not as the result of recurrent hemorrhage or clot formation but as the result of progressively extending cerebral vasospasm.[15] The same phenomenon may also contribute to the development of progressive cerebral edema that may prove fatal.[6,17] These are additional reasons for prompt operation.

RESULTS

As stated above, 4 deaths occurred in our selected group of 35 patients. Case N.S., who was confused and restless prior to operation, was found to have an actively bleeding aneurysm arising from the internal carotid artery at the time of operation. This patient died shortly after operation of massive cerebral edema, in spite of continued hypothermia during the postoperative period. Case R.T. made a good postoperative recovery following clipping of an internal carotid aneurysm only to die some two weeks later of a septicemia secondary to femoral artery catheterization for continual blood pressure recordings. This test was subsequently abandoned. Case C.M. died one month postoperatively from a recurrent hemorrhage, although apparently well when discharged. His internal carotid aneurysm had been packed with muscle and represents the only 1 in this group so treated. Case L.R. died of delayed unilateral cerebral edema after

Fig. 4. (*Case A.D.*) Photograph seven months after excision of large aneurysm of anterior communicating artery. Left hemiplegia before operation. Patient well and normal except for weakness of left hand one year postoperatively.

having made a good immediate recovery. It had been necessary to occlude her right anterior cerebral artery permanently in order to obliterate a large, difficult, anterior communicating artery aneurysm. No decompressive frontal lobe amputation had been done, nor was hypothermia continued into the postoperative period, as is now our practice.

Of 3 patients alive but disabled by neurologic deficits: Case C.L., who was hemiplegic and aphasic preoperatively, remains incapacitated by his severe postoperative aphasia. Case E.S. made a good physical recovery following obliteration of his anterior communicating aneurysm. He is unable to do his usual work, however, because of his slow mentation and poor memory. Case C.L. is incapacitated by upper extremity paralysis following the clipping of her middle cerebral aneurysm. She is mentally intact, however, and able to walk with a leg brace.

The remaining 28 patients, or 80% of our selected group of 35, are well and working at their previous levels of employment. Several of these patients carry some neurologic evidences of their bleeding episodes and/or intracranial surgery, as can be seen from the remarks on Table 1. While postoperative angiograms have only been carried out in 2 of our series (A.D., Fig. 4, and I.B., Fig. 5), postoperative x-rays in all cases have also shown that the permanent occluding clips placed on the necks of their aneurysm have remained closed. No clinical or autopsy evidence has shown any deleterious effects on blood vessels from the use of the temporary intracranial removable clips.

Fig. 5. (*Case I.B.*) Postoperative angiogram showing obliteration of aneurysm of internal carotid artery with tantalum clips. (Three small silver clips are on divided tentorium.)

CONCLUSIONS

Our experience with these 35 selected patients has led us to the following conclusions:

1] Indiscriminate application of any form of therapy to patients harboring intracranial aneurysms is no longer justified. The type of therapy must be chosen according to selection of patients based on their age and neurologic and physical condition and, to a lesser extent, on the location of their aneurysms.

2] Patients who are suspected of having ruptured intracranial aneurysms should have complete arteriography as soon as possible, even if this requires transporting the patient to a center where serial angiography is available. We are aware of no ill effects from such transfers.

3] Patients under 55 years old, who are not in a comatose state when first seen, should be considered for immediate intracranial clipping of their aneurysm under hypothermic anesthesia. In a word, the best expectation for long-term survival for most intracranial aneurysms is produced by their direct obliteration. The earlier this is done, the less the risk of fatal recurrent hemorrhage, permanent hemiplegia, and other neurologic deficits or fatal cerebral edema.

With respect to complications such as the above, strong evidence suggests that cerebral vasospasm—and not hematoma—is often responsible for their occurrence.[15] Furthermore, the full effects of such cerebral vasospasm may not become apparent—in the form of hemiplegia, for example—until the sixth to eighth

day after aneurysmal rupture.[17] For this reason, we feel it is advisable to operate prior to the sixth day following hemorrhage, whenever the age and condition of the patient and the circulatory situation permit.

4] While carotid ligation in the neck may be particularly effective in the treatment of aneurysms arising from the internal carotid artery or adjacent posterior communicating arteries, we feel this technic should be reserved for those patients in whom direct intracranial attack is impossible for medical reasons—such as a bleeding tendency, cardiac decompensation, or the like.

5] Multiple aneurysms do not necessarily represent a contraindication to intracranial surgery as long as angiography and clinical examination establish which lesion is actively bleeding. Severe vasospasm is frequently a clue as to which aneurysm has bled. Of 5 patients with multiple aneurysms in this series, 2 have had bilateral staged aneurysm surgery (I.B. and F.R.) and a third (H.T.) is about to have contralateral craniotomy for this purpose. A fourth (E.C.) has steadfastly refused reoperation or angiography, despite recently developing signs pointing to enlargement of her contralateral aneurysm five years after initial surgery. Her present course, incidentally, indicates the need for treating multiple aneurysms whenever feasible. The fifth case (B.T.) has 7 aneurysms for which further operation is virtually impossible.

6] On the basis of being able to return 80% of a selected group of 35 patients back to full normal activity, relieved of the threat of recurrent bleeding, we believe that many lives can be saved and permanent neurologic deficits averted by prompt intracranial attack on suitable aneurysms of the circle of Willis. It also appears that more lives can be saved by operation within the two-month critical period than by conservative therapy in selected patients.

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Migraine plus epilepsy

Walter C. Alvarez, M.D.

As I NOTED in another paper, whenever I see a patient with a severe, bizarre, or long-lasting migraine refractory to treatment, I suspect that I am dealing with migraine plus something else —such as a mild psychosis, an unrecognized epilepsy, a cerebral arteriosclerosis, or a constitutional inadequacy. Elsewhere, I have described a series of patients with migraine plus a mild psychosis. Now I present cases in which migraine was complicated by a mild epilepsy or an epileptic carrier state.

In 1912, I saw a man in his thirties with a migraine so severe that I suspected the presence of an extra component. I learned that he had a brother whose life has been ruined by epilepsy. I put my patient on the then-used bromides, and he was much relieved. Ever since then, whenever I have seen a patient with an unusually severe migraine, or migraine that persisted in a severe form into the patient's later years, I have asked if he had epileptic or violent-tempered or psychotic forebears, and often I have learned that he had some. I am particularly suspicious of an epileptic component when the patient keeps getting severe migraines without any obvious exciting cause. Then I wonder if the triggers could be little epileptic storms in the brain, and, when I get electroencephalograms made, I may find the expected signs of seizure activity. As most physicians know, in cases of pure migraine in which no epilepsy occurs in the patient's family, the electroencephalograms are normal.[4]

Are migraine and epilepsy related? Several authorities have claimed that migraine and epilepsy are related, but I cannot believe this.

1] The 2 diseases usually appear in different types of persons with different temperaments.

2] Migrainous persons, who know of no epilepsy or psychosis in their family, usually have normal electroencephalograms.

3] Anticonvulsive drugs do not help the person with a pure migraine.

4] Persons with ordinary, mild migraine rarely have epilepsy or epileptic relatives.

However, when I went at the investigation the other way around and started with relatives of epileptics, I found 21% had had sick headaches.[1] In 1933, Peter Bassoe, starting with 200 epileptic patients, found that 28% had some migrainous relatives.[2] Like me and some others, he had found very few migrainous patients with epilepsy or with epileptic relatives.

At first glance, the high incidence of migraine among the relatives of epileptics suggests a relationship between the 2 diseases, but when I studied the relatives of 574 psychotic and alcoholic patients, I found that 23% had had migraine. So far as I know, no one has suggested that migraine is related to psychosis; in fact, as some observers have noted, most migrainous persons are unusually sensible and sane.

The probable explanation for the figures obtained is that, when migraine is uncomplicated, a high percentage of the patients have such a mild syndrome that they never mention it to a physician. But when patients have migraine plus a mild psychosis or epilepsy, the syndrome is usually so severe and incapacitating that when they visit a physician they will surely complain about it.

The incidence of migraine. Unfortunately, no one can guess what the incidence of migraine is in the United States or in any particular group within the United States. No 2 men agree on what is mild migraine, and most of them diagnose the disease only in its less common severe forms. Because migraine is a disease of bright, wide-awake, well-educated persons, the incidence in any particular group must depend on the average education and social position of the people in the group. The figures to be found in the literature range from 1.6 to 53%.

Reported cases of migraine plus epilepsy. In his great book, *Megrim and Sick Headache* written in 1873, Edward Liveing, mentioned families in which migraine was mixed with

psychosis and epilepsy.[3] He told of a migrainous woman with an epileptic brother and sister. He said, "Her own Megrim, after recurring regularly once a month for 23 years, was replaced by epilepsy." Another patient "had a sister, epileptic, and her own Megrim was replaced after two years by epilepsy."

Other cases have been reported in which migraine and epilepsy alternated, but I think what the stories mean is that 2 diseases were inherited by 1 person. Often when asked about this, the patient will say, "Yes, that's right; I got my migraine from one ancestral group and my epilepsy from the other."

CASE REPORTS

Following are reports of a number of patients with 2 inheritances. Several of these reports would be more convincing if I could say what the electroencephalogram was like, but, unfortunately, in many cases, the patient was from out of town, could not wait for an appointment to get an electroencephalogram, or did not feel he could afford one.

Why the case histories are brief. To those many readers who may be distressed because in the following abstracts of case histories I do not give details about physical, laboratory, and x-ray findings, I will say that *all* these people were thoroughly examined in several great medical centers, usually several times, and nothing pertinent was found besides what I mention here. I do not see any sense in wasting many pages on purely negative findings. Actually, during the hundreds of careful and extensive studies made on migrainous persons, I rarely found any organic disease and very rarely found any organic disease that could explain the frequency of the spells. Migrainous attacks come out of a hereditarily predisposed brain and are seldom worsened by any disease below the neck. In a few patients marked hypertension was perhaps causing the attacks to come more frequently. Many of the women patients had had their gallbladder or a myomatous uterus removed, but none had been cured.

The evidence given here is suggestive. In the cases now to be reported, I cannot *prove* that the severity of the migrainous spells was due to the extra factor of an epileptic inheritance; but, in most of my patients in whom migraine was particularly severe, I suspect it was because I found an extra psychotic or epileptic element in the person's illness or heredity. In medicine, when one keeps observing something again and again, it is likely to be significant.

EPILEPSY IN THE FAMILY

A young woman with a terrible migraine had a mother with a history of seizures which were apparently epileptic in nature. Of her 2 sisters, 1 was depressed and 1 had a violent temper. My patient's brilliant brother was drinking himself to death. In this case, my impression was strong that my eccentric and violent-tempered patient was a carrier of epilepsy.

A woman with one of the worst migraines I ever saw had a lot of queer relatives. Her migrainous father had an epileptic nephew and a psychotic great-nephew. The migrainous mother had a psychotic sister (who had a hysterectomy when she was 20) and also an insane first cousin. My patient had a sister and a brother both with violent tempers—such as one finds in some epileptic patients. The sister had a crazy, alcoholic daughter and 2 alcoholic sons.

An attractive, able, unmarried business woman of 50 had had frequently recurring and severe migraines for 37 years. Her mother was "a devil" with a terrible temper. Several members of the mother's family were much like her—some of them alcoholic and some insane. On the patient's father's side, there was epilepsy. It was not surprising that a woman with such poor genes on both sides of her family should have had a stormy temperament and a life racked by violent emotions.

An unmarried woman of 26 said that, although her severe migraines no longer occurred, she still suffered so grievously from spells of paralyzing fatigue (suggesting migraine) that she could not hold a job. She was afraid to marry because her health was so frail. Among her near relatives were several epileptics and alcoholics.

MEN WITH SEVERE MIGRAINE

A man who was pleasant and good-tempered began with severe, migrainous headaches at the age of 48. I suspected a connection be-

tween this severe and late-coming migraine and his poor nervous inheritance. His father's brother drank himself to death, and his father, a confirmed grouch, had an ungovernable temper which suggested an epileptic carrier state. The child of this father's sister had epilepsy, and my patient's sister and brother were epileptic. Unfortunately, I could not get an electroencephalogram made.

A business man was still having severe migraine at the age of 45. With the headache, he had short explosive attacks of diarrhea, such as many psychotic persons have. When I asked him where he had gotten a poor nervous inheritance, he said his mother and her 2 sisters were insane and his sister's child had epilepsy. I regret that the man would not stay to let me get an electroencephalogram made.

At the age of 50, an intelligent, odd-looking scientist was still having terrible migraines 2 or 3 times a week. Often the pain was so unbearable he had to take 3 or 4 injections of morphine. He had a somewhat dysrhythmic electroencephalogram. His work kept him tense, but this didn't seem to be enough to explain all the trouble. All his sibs had an epileptic type of violent temper, and 1 sister was psychotic. My impression was that the great irritability of his nervous system was due to a tendency to epilepsy.

A highly sensitive, 40-year-old man was still suffering from severe migraines with nausea and vomiting. His mother's father had epilepsy.

PERSONS WITH MIGRAINE PLUS EPILEPSY OR WHAT APPEARED TO BE EPILEPSY

In this section, I am describing cases in which a migrainous type of headache was particularly severe in the case of a woman or man who suffered from either definite epilepsy or what looked like an epileptic carrier state. Sometimes the person had a violent temper and sometimes a dysrhythmic electroencephalogram.

Very interesting to me was the problem of a 24-year-old man who had been complaining of terrible unilateral headaches and vomiting for eight years. The pain in his head was so severe that sometimes he screamed. He had no typical scotoma, but, in the spells, his eyes were very sensitive to light. For two days before a spell, he would have a migrainous type of aura in which he was unusually amorous. Sometimes he had a constant type of headache, such as one sees in some relatives of psychotic patients. During many spells, he would be apathetic and would keep rubbing his left eye with the back of his hand as if he were in an attack of psychomotor epilepsy. As a boy, 1 eye tended to turn in. Several able internists who had studied him carefully had recognized the migrainous element in his illness but had been unable to help him with ergotamine.

Only after 3 talks with the man's father did I draw out the reluctant admission that, from boyhood on, the patient had been epileptic. Occasionaly, he would be found lying unconscious on the floor. After several more talks with the father, I learned that the young man had lost jobs because of falling down at work. He had a violent temper, and, as I expected, Dr. Gibbs found a typically epileptic type of dysrhythmic electroencephalogram. His father and his father's father were fiery-tempered and could have been carriers of epilepsy. The mother was an able woman—a carrier of migraine. After administration of Dilantin, the young man made an immediate and remarkable recovery. After a few years, he reported that he could get by without the anticonvulsive drug.

One of the worst cases of intractable migraine I ever had to deal with was that of a young, quick-tempered, married woman whose attacks were so severe that sometimes she would vomit for days and become unconscious. The only thing that would relieve her was methadone. Her face often twitched, even when she wasn't in a spell. I could not get a history of bad heredity, but almost all the members of her family were neurotic. The fact that her electroencephalogram showed a marked dysrhythmia suggested that she was a carrier of epilepsy. Unfortunately, she was no better on anticonvulsive drugs.

Another woman with such a severe migraine that I could not help her much also had a markedly dysrhythmic electroencephalogram. Her father had been a good-for-nothing who had deserted his family. Because the woman came from a great distance, I do not know if

she was helped with the Dilantin I prescribed.

A woman of 44 had severe migraine, severe epilepsy, and a dysrhythmic electroencephalogram. From time to time, she had a hysterical type of contraction of a segment of muscle in the left upper quadrant of her abdominal wall. For five or ten minutes, the muscle would feel like a door knob. She also had spells of hysterical bloating. From 10 to 20 times a day, she had transient jabs of abdominal pain—typical equivalents of epilepsy. Because of these pains, a surgeon had explored her abdomen on two occasions—to no purpose.

A woman's very severe migraine was a puzzle to me until I learned of queer spells she was having which almost certainly were equivalents of epilepsy. Also, I learned that once she had had an attack of grand mal in which she had fallen heavily. Her mother had fainting spells, apparently epileptic in nature.

A pleasant, nice-looking, married woman was still having occasional severe, prostrating attacks of migraine at 45. For years she had had epileptic seizures and attacks of nervous bloating. Her father drank heavily. Her son was an epileptic, but possibly he got at least some of his trouble from his father who appeared to be a carrier of epilepsy.

A highly migrainous divorcée of 50 was sickly and complaining, always hypochondriac, often unable to work, and often getting herself operated on for some supposed disease. Her story of severe convulsions, temper tantrums, and terrible nightmares in infancy suggested that she had had epilepsy in her childhood. She admitted she had had such a violent temper that several husbands in succession had walked out on her.

A woman with a severe form of migraine had a mild epilepsy and a dysrhythmic electroencephalogram. Occasionally, she had a short spell of diarrhea. Perhaps, as an equivalent of migraine or epilepsy, she had spells of nausea lasting two weeks at a time. She had a number of alcoholic and psychotic relatives, plus some relatives who behaved like highly irritable carriers of epilepsy.

At 51, an unhappy divorcée was still having severe migraines. She had a dysrhythmic electroencephalogram and a number of epileptic forebears.

A man of 39 told me that, in his early years, he had had very severe migraines. Later, they changed into spells of dizziness, with "almost blackout" and with feelings of fear that he would shake all over and fall down. After much questioning, I learned that in his youth he had had episodes of grand mal. At times he was alcoholic. Epilepsy ran through his father's family.

A man of 52 with terrible migraines looked like a sullen, degenerating type of epileptic. He was so irascible that he was often discourteous to customers in his store. As I expected, he had a dysrhythmic electroencephalogram. He had a migrainous mother, an insane brother, and another brother who had an idiot child.

Diagnosis was difficult in the case of an intelligent, nervous, and typically migrainous married woman who, in her early years, had had frequent sick headaches. After the age of 30, her syndrome changed and consisted of spells of great distress in her abdomen. This interfered so much with her breathing that she often felt as if she were choking. For years these spells were severe and long-lasting. They would come at any time of day or night. She could not identify any triggering cause. At times she would regurgitate her food.

Eventually, I drew out the story that one night, three years before I saw her, her mother had heard her thrashing about and had found her in a fit. She was hard to waken, and, next morning, like an epileptic, she had no memory of the episode. Later, she had another similar spell and, following that, a series of spells that resembled petit mal. Suggestive of an epileptic carrier state were such facts as that she and her mother both had violent tempers and that the mother's nephew was epileptic. My patient's father was a drunkard. Unfortunately, I could not get her to stay for the making of an electroencephalogram.

A middle-aged, highly irritable woman had had severe migraines in her childhood. When I saw her, she had what looked like an epileptic carrier state. In her childhood, she had had terrible nightmares, frequent tantrums, and spasms of rage and had always been rebellious —refusing to do anything she was asked to do. She walked and talked in her sleep. She

had severe chorea at the age of 12. At the age of 17, she contracted a foolish marriage and soon was deserted by her husband. For a while after that, she drank a pint of whiskey a day. Then she went into a depression. In later life, she had a severe constant pain around her rectum—a pain such as one sees in some mildly psychotic persons. Her grandfather, who came of insane stock, was a restless man with severe migraines. The patient's sister went insane after years of alcoholism. She had alcoholic uncles on both sides of the family. I could not learn of any epileptic relatives. With her stormy, emotional nature, this woman's migraines should have been severe—and they were.

MILD MIGRAINE AND AN EPILEPTIC INHERITANCE

The next few reports are inserted here just to show that in some cases an epileptic or a person with an epileptic inheritance can have a mild type of migraine.

A 48-year-old woman had a mild migraine in spite of the fact that twice a year she had an attack of grand mal. She had a typically epileptic electroencephalogram. Her mother who was epileptic and diabetic had a sister who was insane. The patient's sister was at times depressed.

A woman with mild migraine had a mild epilepsy with some dysrhythmia in her electroencephalogram. Her hot-tempered father was depressed at times, and his father was alcoholic. The patient's brother was diabetic and hot-tempered. Her mother was migrainous.

A 24-year-old woman with mild migraine and a dysrhythmic electroencephalogram was subject to attacks of grand mal. She had several psychotic relatives but knew of no epileptic ones.

A woman with a mild migraine complained only of short spells of depression. She probably was a carrier of epilepsy because her father's mother was epileptic, and she (the patient) had an epileptic child. Her father's sister was insane, and a great-grandfather drank himself to death.

SUMMARY

When one has to deal with a person with unusually severe migraine or migraine still severe in the person's later years, one should think of a second component—which sometimes is epilepsy or an epileptic carrier state.

The writer gives several reasons for his inability to accept the thesis that migraine is closely related to epilepsy. It seems more probable that, when epilepsy and migraine are found together in a patient, they are due to 2 inheritances.

Persons with simple or typical or mild migraine seldom have epileptic relatives, but in a study made by the author, 21% of 99 relatives of epileptics had had migraine. This does not prove a relationship between the 2 diseases, because, in a group of 574 relatives of psychotic or alcoholic persons, 23% were found to have migraine, and migraine and psychosis do not appear to be at all related. Persons with pure migraine have normal electroencephalograms, and they are not helped by anticonvulsive drugs. Persons suffering from migraine are usually very different—physically, intellectually, socially, and temperamentally—from persons suffering from epilepsy.

A series of cases are described in which persons with a severe form of migraine had either what looked like an epileptic inheritance or actual epilepsy in themselves.

It is well to recognize epilepsy when it is added to migraine because epilepsy can explain so easily the severity of the syndrome and occasionally can lead to a cure with the help of anticonvulsive medication. A few epileptic patients will be found to have mild migraine.

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Effect of drugs on discharge characteristics of chronic epileptogenic lesions

Frank Morrell, M.D., William Bradley, M.D.,
and Mark Ptashne

MOST EXPERIMENTAL evaluations of anticonvulsant drugs have been done through the use of acute preparations employing seizures induced by electroshock or by Metrazol. While such measurements provide valuable basic screening for potential anticonvulsant compounds, they do not permit detailed analysis of anticonvulsant action over an extended time period. It seemed, furthermore, that the animal with a chronic epileptogenic lesion was more closely related to the usual clinical situation than either Metrazol or electroshock challenge.

A modification of the freezing principle has been developed which employs a fine jet of ethyl chloride spray applied to a 1- to 2-mm. area of cortex.[1] The technic will be outlined in detail elsewhere. The method has now been used in 68 rabbits and cats and has produced reliable epileptogenic foci in 55 animals. Seizure discharges began approximately three hours after application of the spray and persisted as a well-defined focus for at least six months—the maximum period of observation so far. Whether or not clinical symptoms appeared depended, of course, on the site of the focus, intensity of discharge, and preferential pathways of spread.

One of the major difficulties in evaluating drug effects in chronic preparations is the natural, day-to-day variation in the interictal spike dsicharge. The cause of this variation is unknown, but the fact has been emphasized by Kennard[2] and by the Kopeloffs.[3] In our own preparation, we also noted long-term, day-to-day variation in spike discharge frequency. However, we noted that, in a given animal, spike frequency was remarkably constant from three to twelve hours after initial development of the discharge. We therefore chose to make our preliminary measurements during this early phase.

Spike frequency was used as one parameter of drug evaluation. The kind of discharging lesion obtained is illustrated in Figure 1. The discharge frequency at four hours (B) may be compared with the discharge frequency at eight hours (C) after producing the epileptogenic lesion. Although the discharge frequency varies from 3 to 5 per second, a count of the number of spike discharges in thirty-second epochs shows less than a 10% variation in the total count when such thirty-second epochs are compared. The spike frequency then was taken as a measure of the activity of the primary focus.

Other parameters observed were amount and rapidity of spread both transcortically and to basal nuclei, activation of spike discharge by photic stimulation, and protection against acute Metrazol challenge. The latter was employed at the end of the experiment in each animal in order to compare our results with data from other pharmacologic studies on animal convulsions. The drugs used were phenobarbital, Dilantin, Tridione, and 3,4 dihydro-2-)1, 4) naphthalenone hydantoin (Spirodone). Phenobarbital was given in doses of 50 mg. per kilogram; Dilantin, Tridione, and Spirodone were administered in doses of 100 mg. per kilogram. All drugs were administered intraperitoneally after establishment of the stable focal discharge and recording of the control discharge frequency. The rabbits were divided into 4 groups of 12 animals each; each group was given one of the drugs. The animals were, of course, given no medication other than the

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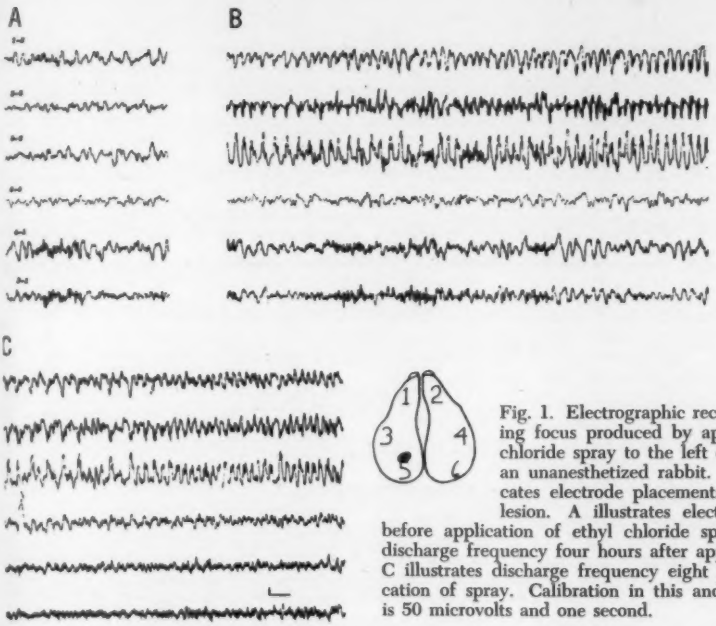

Fig. 1. Electrographic record of a discharging focus produced by application of ethyl chloride spray to the left occipital region in an unanesthetized rabbit. Inset figure indicates electrode placements and area of the lesion. A illustrates electrographic pattern before application of ethyl chloride spray. B illustrates discharge frequency four hours after application of spray. C illustrates discharge frequency eight hours after application of spray. Calibration in this and all other figures is 50 microvolts and one second.

drug being studied. They were restrained in a comfortable harness, and electrical recording was done through implanted dural electrodes. All focal lesions were made in the left occipital region and anatomically confirmed after sacrifice.

RESULTS

In this preliminary report, we shall review only the most clearly established findings for each of the drugs studied.

Effect on discharge frequency of the primary focus. Figure 2 demonstrates the effect of phenobarbital on the primary spike focus. The discharge frequency without drugs (B) may be compared with the resting electroencephalogram of the same animal before the epileptogenic lesion was produced (A) and with the discharge frequency of the focus one and one-half hours after the intraperitoneal injection of 50 mg. of phenobarbital per kilogram (C). Spike discharge is clearly not suppressed and, indeed, has somewhat increased in amplitude. Injection of 10 mg. of Metrazol per kilogram produces marked local activation of the focus, but no spread of the abnormality to other areas (D).

Contrast this with the effect of Spirodone. Figure 3 is a comparison of the predrug discharge frequency (A) with the electrical record at two hours (B) and three hours (C) after intraperitoneal administration of 100 mg. of Spirodone per kilogram. A remarkably complete suppression of the primary spike discharge occurs. The slow component remains to indicate the abnormality at the site of the lesion.

The effect of Tridione on the chronic epileptogenic focus is illustrated in Figure 4. The predrug discharge pattern (B) may be compared with the resting electroencephalogram (A) before production of the epileptogenic lesion and with the tracing (C) taken twenty minutes after intraperitoneal administration of 100 mg. of Tridione per kilogram. The effect in twenty minutes was a clear-cut activation of the focal discharge and an extensive spread of this discharge along the ipsilateral cortical surface. The contralateral hemisphere shows relatively little involvement. This latter fact

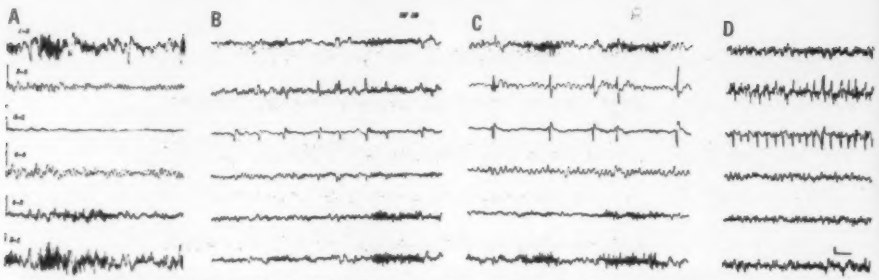

Fig. 2. Effect of phenobarbital. (A) Electrographic pattern before establishment of epileptic focus. (B) Resting discharge pattern of the epileptic focus before administration of drug. (C) One and one-half hours after intraperitoneal administration of 50 mg. of phenobarbital per kilogram. (D) Effect of injection of 10 mg. of Metrazol per kilogram in the same animal. Note that Metrazol produces marked local activation of the focus but no spread of the abnormality to other areas.

Fig. 3. Effect of Spirodone on local epileptiform discharge. A indicates the predrug discharge pattern, B is two hours after administration of 100 mg. of Spiridone per kilogram, and C is three hours after administration. Electrode placements are the same as in previous figures.

and the slow, rather than abrupt, spread along the cortical surface, which is successively picked up in leads at greater and greater distance from the focus, are taken as evidence that the dissemination of paroxysmal activity seen in the earliest stage of Tridione effect is by contiguity along the cortical surface and not to the basal or midline nuclei.

Although this early activation of the focus and augmentation of spread were characteristic, transient effects of this drug, they were rapidly replaced by a marked suppression of the focal discharge and a normalization of the record which was more pronounced than with any of the other drugs tested. The electrical record two hours after the injection of Tridione, (D) shows very little abnormal activity. However, injection of 20 mg. of Metrazol per kilogram (E) demonstrates that the focal area is still abnormal. The focus itself was reactivated, but neither generalized paroxysmal discharge nor a clinical seizure was produced. In fact, this animal was completely protected (no convulsions) after a test dose of 100 mg. of Metrazol per kilogram administered intramuscularly.

Photic activation. The fact that these were all occipital foci provided 2 advantages. First, the distance from the motor cortex made it possible to observe considerable change in the focal discharge before motor symptoms appeared, and, often, no motor manifestations occurred at all. Second, the lesion was particularly sensitive to activation by flashing light, and, thus, a method was available by which drug effects could be measured against a relatively standard stimulation of the lesioned cortex.

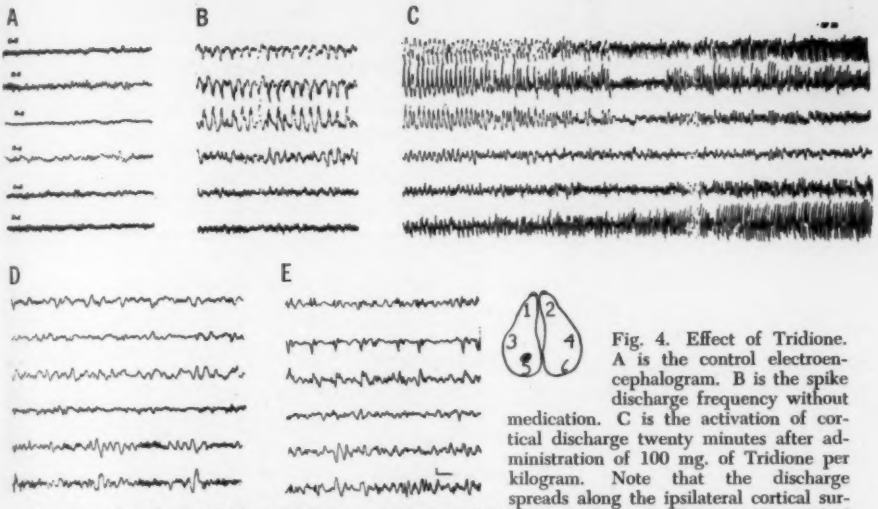

Fig. 4. Effect of Tridione. A is the control electroencephalogram. B is the spike discharge frequency without medication. C is the activation of cortical discharge twenty minutes after administration of 100 mg. of Tridione per kilogram. Note that the discharge spreads along the ipsilateral cortical surface but that there is little involvement of the contralateral hemisphere. D illustrates the marked suppression of the focus which occurred in the same animal two hours after injection of Tridione; very little abnormality is seen. In E, abnormality of the focal area is still demonstrable, however, by injection of 20 mg. of Metrazol per kilogram which reactivates the local discharge.

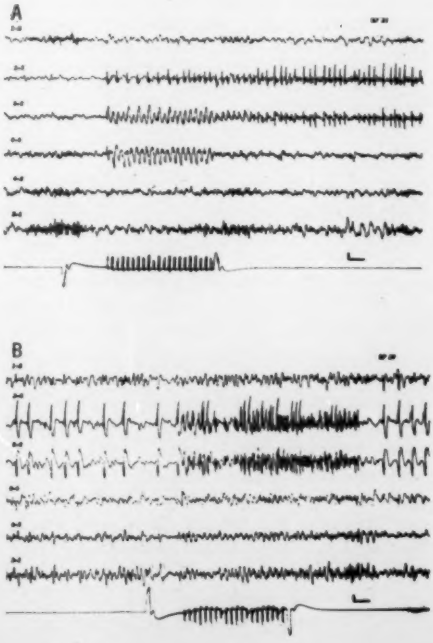

Fig. 5. Threshold to flicker activation. (A) Activation of focal discharge in an animal under 100 mg. of Tridione per kilogram. This recording is two hours after administration of Tridione, and there is no abnormality in the resting tracing before photic stimulation is begun. Photic stimulation then elicits driving on the normal cortex and activation of the seizure discharge which continues as an after-discharge on the abnormal cortex. Note that the discharge remains limited to the local region. (B) Another animal under 50 mg. of phenobarbital per kilogram. In this case, the focal discharge is quite evident but is made much more active by the photic stimulation which, in addition, produces an after-discharge. This is of short duration, and the prestimulation discharge frequency soon returns.

None of the drugs employed prevented activation by flicker, but all of them considerably reduced propagation of the discharge which, even when local after-discharge was present, remained limited to the abnormal occipital region. Figure 5 demonstrates flicker activation in an animal two hours after administration of Tridione (A) and in another animal two hours

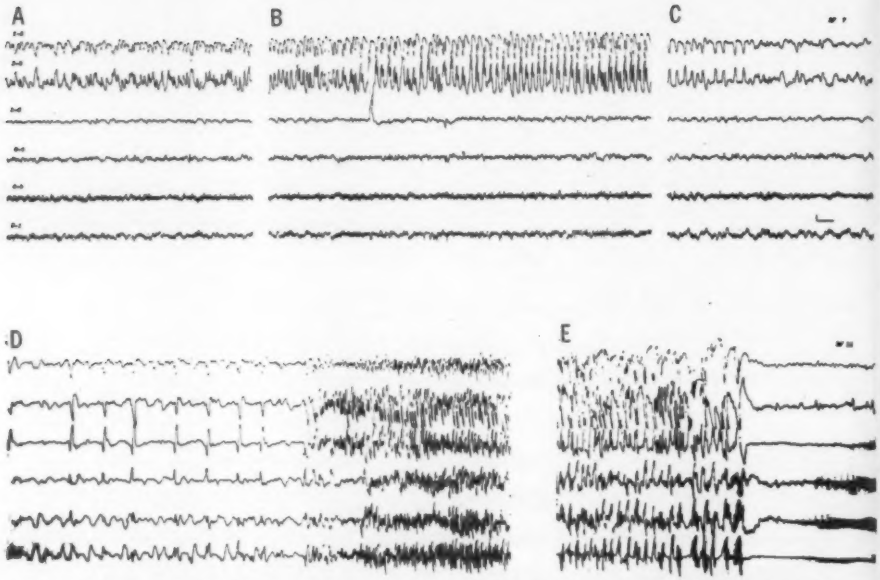

Fig. 6. Effect of Dilantin on primary focus. (A) The primary focus and the gradual development of a local seizure discharge. (B) Ten minutes later, the discharge continues to be very active and is associated at this time with clonic movements of the contralateral forelimb. Note the lack of spread to the contralateral cortex. (C) The end of the local seizure discharge. (D) The local discharge in another animal which is augmented by injection of Metrazol. Little transcortical spread occurs until, suddenly, a bilateral synchronous discharge appears in all cortical leads. A tonic-clonic seizure then developed which ended (E) with simultaneous suppression in all cortical regions.

after administration of phenobarbital (B). Note the prominent after-discharge and the lack of tendency to spread.

Effect on propagation. Observation of the effects of Dilantin on the electrographic pattern provided some data on differences in drug effect regarding spread of seizure activity. Dilantin administered in doses of 100 mg. per kilogram produced no evidence whatsoever of suppression of the primary focus (Fig. 6). This was true even when recording was continued for twenty-four hours. Frequently, a local seizure discharge was observed which continued for many minutes without showing any propensity for spread. Such a seizure is illustrated in Figure 6; the electrographic discharge is indicated at onset (A), ten minutes later (B), and twenty minutes later (C). During the period of most active discharge (B), associated clonic twitching of the contralateral forelimb occurred. At no time was the contralateral cortex involved nor did generalized seizure occur. On the other hand, intramuscular administration of 20 mg. of Metrazol per kilogram caused activation of the focus (D) with very little transcortical spread —until, suddenly, a bilateral, synchronous discharge appeared in all cortical derivations. This was accompanied by a clinical tonic-clonic seizure and followed by signs of cortical exhaustion in all areas (E). It would seem, therefore, that, while Dilantin suppresses transcortical spread, the drug does not prevent the spread to the basal nuclei which is responsible for the bilateral synchronous paroxysm. Dilantin offers no protection against Metrazol challenge and does not suppress the primary focus.

Figure 7 summarizes the data on suppression of the primary focus for each of the anticonvulsants investigated. Counts of the number of spikes in a thirty-second epoch were made every twenty minutes for four hours and are recorded as a percentage of the control spike frequency—which is taken as 100%. Each point represents a mean of the 12 animals in each drug group. Differential effects of these agents as a function of time seem especially noteworthy. There is a phase of increased activity in the early portion of the Tridione curve, and, at one and one-half hours, in the curve depicting the effect of phenobarbital.

Tridione had the most profound ultimate effect on the primary discharge, and Dilantin, the least. Increased excitability did not occur with Spirodone. The table summarizes the over-all results. The number of pluses is a rough indication of relative effects.

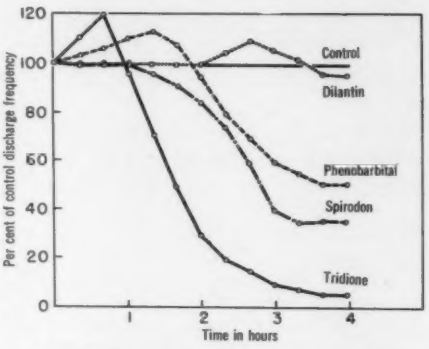

Fig. 7. Graph of the effect of various drugs on frequency of spike discharge in primary focus.

CONCLUSION

It is interesting that the clinical anticonvulsant effect could be best correlated with limitation of spread rather than with suppression of the primary focus. Possibly, the greater part of the anticonvulsant mechanism is the reinforcement of those intrinsic systems within the brain which serve to limit propagation, rather than in direct action on epileptogenic tissue. Evidence that Dilantin alters glutamine-asparagin metabolism[4] may indicate that these latter compounds play a role in intrinsic limiting systems of the brain rather than acting directly on epileptiform electrogenesis.

The differences in the pattern of spread for each of these drugs may indicate different anatomic sites of action. For example, the early, increased transcortical propagation seen under Tridione may reflect a primary depression of diencephalic inhibitory systems. The fact that Tridione clearly prevents spread to the diencephalon and is the most effective protection against Metrazol supports that assumption. Suppression of epileptiform activity in both cortex and diencephalon is consistent with the observation of Gangloff and Monnier[5] on a similar effect of Tridione as measured by after-discharge to electric stimulation of these structures. However, our findings regarding Dilantin do not suggest a depression of diencephalic excitability, as is indicated by the findings of these authors. Since range of doses used in these 2 studies is comparable, the discrepancy probably reflects differences in the mode of measurement. However, since the clinical effectiveness of Dilantin is in such striking contrast to its lack of suppression of the primary epileptic focus, more attention might usefully be devoted to an analysis of those central mechanisms which tend to prevent the development of cell synchronization and the recruitment of ever-widening ganglionic regions. A good deal of the mechanism of action of anticonvulsants may be related to the bolstering of such intrinsic limiting sys-

SUMMARY OF DRUG EFFECTS ON SEIZURE DISCHARGE

Drug	*Suppression of primary focus*	*Limitation of spread*		*Metrazol protection*
		Basal	*Cortical*	
Dilantin	O	O	++	O
Spirodone	++	+	++	+
Tridione	++	++	O	+++
Phenobarbital	+	++	+	+++

tems rather than to any effect on the threshold of various cortical regions to electrical or to epileptic activation.

SUMMARY

Chronic epileptogenic lesions were produced in the visual cortex of rabbits. The effect of anticonvulsant agents was measured against the discharge frequency of the spike focus, the threshold to photic activation, and the characteristic patterns of spread. A standard Metrazol challenge was used as a means of comparing our results with those obtained in the more usual pharmacologic assays. Dilantin did not produce suppression of the primary focus nor did it appear to limit spread to the basal diencephalon or to protect against Metrazol challenge. However, transcortical propagation was effectively limited.

Spirodone demonstrated effective suppression of the primary focus as well as limitation of spread both to basal nuclei and transcortically. Some protection also existed against Metrazol challenge. Tridione also appeared to suppress the primary focus as well as to limit spread to the basal diencephalon. However, transcortical spread was not effectively limited until the primary focus itself was suppressed. Metrazol protection was the highest of any of the drugs tested. Phenobarbital produced only slight suppression of the primary focus and transcortical spread, good limitation of spread to the basal diencephalon, and good Metrazol protection.

ACKNOWLEDGMENTS

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Lee M. Eaton

With a sobering sense of personal loss, this memoir is dedicated to Dr. Lee M. Eaton as a testament to his twenty-five years of devoted work in clinical neurology.

JOE R. BROWN

Lee Eaton died on November 18, 1958, of myocardial infarction at the age of 53 years. Although, as his colleagues, working in intimate association with him, we were aware that he had had earlier episodes of anginal distress, we were entirely unprepared for his abrupt death. Possibly, influenced by his own incessant labors in the field, we had somehow come to believe that neurologists were indestructible. Lee had been for those of us in neurology at the Mayo Clinic our teacher, colleague, chief, and, above all, our warm friend.

He was born on February 3, 1905, in Owaneco, Ill. He took his early schooling there and also at Decatur. After two years at James Millikan University in Decatur, he transferred to the University of Chicago, where he received the degree of bachelor of science in 1927. He obtained his medical education at Rush Medical College, University of Chicago, graduating in 1932. He then interned for a year at Cook County Hospital.

In 1933, when the country was in the depths of the depression, Lee was appointed a fellow in internal medicine in the Mayo Foundation at Rochester, Minn. One of his early assignments was to the Section of Neurology of the Mayo Clinic, under the tutelage of Drs. Walter D. Shelden, Henry W. Woltman, and Frederick P. Moersch. As a result of this stimulating experience, he transferred his interest to the field of neurology, despite the poor economic outlook for neurologists at that time. In 1938 he was appointed to the staff of the Mayo Clinic as a consultant in neurology and achieved steadily widening recognition until he was advanced to the rank of professor in neurology in the Mayo Foundation in 1950 and to the chairmanship of the Section of Neurology of the Mayo Clinic in 1955.

Lee was one of the founding members of the American Academy of Neurology, and he looked upon it as a vital force in the development of the field. He was successively secretary and president (1953) of the Central Neuropsychiatric Association and served as chairman of the Section on Nervous and Mental Disease of the American Medical Association in 1956. Other organizations of which he was a member included the American Neurological Association, the Advisory Board of the Myasthenia Gravis Foundation, Alpha Omega Alpha, and the Society of the Sigma Xi. At the time of his death he was president of the Association for Research in Nervous and Mental Diseases, and he had been elected a member of the American Board of Psychiatry and Neurology, Inc.

His writings were extensive, touching on numerous clinical neurologic subjects. In re-

cent years his investigative efforts had been directed toward myasthenia gravis and polymyositis. These efforts led subsequently to contributions to the broader aspects of diseases of the motor unit. Although his strongest orientation was clinical, he devoted many evenings to the microscopic study of muscle and he also had familiarized himself with various aspects of electromyography.

Lee Eaton was first and foremost a fine physician who applied the subtle technics of a neurologist to the care of patients. As a teacher of these technics he gained the enduring respect of the fellows in graduate training at the Mayo Foundation. An able administrator, he continued the development of the Sections of Neurology of the Mayo Clinic and stimulated the maturation of his younger colleagues. The inevitable objective of his research was improvement in the care of patients.

In his personal life, he was active in community affairs, and he maintained a continuing enthusiasm for hunting, boating, photography, and the Chicago White Sox. Mary Lou (Long) Eaton, whom he married on April 2, 1936, five children, and one grandchild were the proud and warm focus of his life.

Those who knew Lee will remember him for his unfailing thoughtfulness, helpfulness, and friendliness.

CASE REPORT

Chromophobe adenoma of the pituitary

Clinicopathologic report of a case

Leopold Liss, M.D., and Robert S. Jampel, M.D.

CHROMOPHOBE ADENOMAS of the pituitary gland are rare in children and adolescents. Zulch[1] stated that pituitary adenomas practically never occur in persons less than 20 years old, and Cuneo and Rand[2] did not find any hypophyseal adenomas in a study of 83 intracranial neoplasms in children. However, chromophobe adenomas are observed in young persons sporadically. In Cushing's[3] series, the youngest patient with a chromophobe adenoma was 18 years old. Kernohan and Sayre[4] reported that, in a study of 565 chromophobe adenomas, 22 patients were less than 20 and 1 was less than 8 years old. The present case illustrates some important clinical considerations and unusual pathoanatomic findings.

CLINICAL HISTORY

The patient was a 14-year-old girl who, at the age of 3, had had an operation for strabismus at another clinic. She was first seen at University Hospital in February 1953, at the age of 10. At that time, examination revealed a visual acuity of 20/100 and Jaeger type 7 in the right eye and 20/20 and Jaeger type 0 in the left eye. Conjunctival scars were noted over the insertions of the medial recti. About 10° of right esotropia and poor alternation prevailed. The left eye was preferred for fixation. Extraocular muscle examination revealed overaction of the inferior oblique and underaction of the right superior oblique. Convergence power was fair. Ophthalmo- and biomicroscopic examinations were normal. Full cycloplegic correction had no significant effect on the angle of the strabismus. A diagnosis of right convergent strabismus, suppression amblyopia of the right eye, overaction of the right inferior oblique, and weakness of the right superior oblique was made.

The patient returned to University Hospital in November 1956, at age 14, because a local optometrist was unable to bring the visual acuity in the left eye to normal. She complained of daily, bitemporal headaches. Menses had been irregular since onset at age 11. Ophthalmologic examination at that time revealed a corrected visual acuity of 20/100 and Jaeger type 7 in the right eye and 20/40 and Jaeger type 1 in the left eye. Pupillary reflexes were normal. The extraocular muscles had not changed since first examination. Ophthalmo- and biomicroscopic examinations were normal. Tangent screen examination showed tubing and spiraling (Fig. 1). Neurologic and general physical examinations revealed no significant abnormalities. Skull roentgenograms were not made.

The mother was oversolicitous, and the child was tense and anxious. This, plus the field findings and normal ophthalmoscopic and neurologic examinations, led to the impression of ocular hysteria.

However, the headaches and irregular menses persisted and examination was repeated in March 1957. She complained of decided loss of vision in the right eye and some loss in the left eye. She was able to detect movement in the upper nasal field of the right eye. Acuity of the left eye was 20/40 and Jaeger type 1 with correction. Testing of pupillary reflexes revealed a pseudoanisocoria on the right. No new abnormality of the extraocular muscles was detected. Ophthalmoscopic examination disclosed primary type optic atro-

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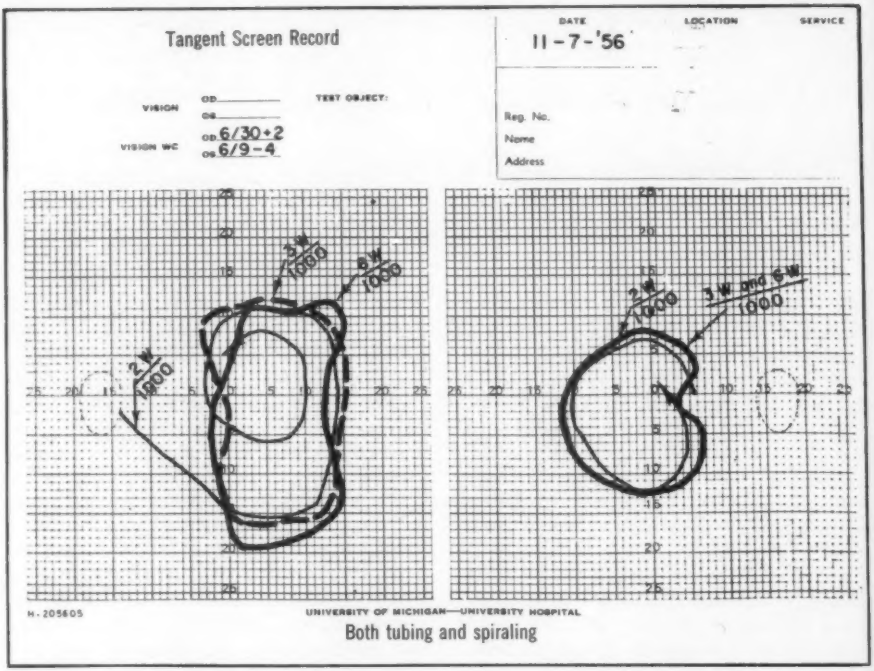

Fig. 1. Tangent screen record showing tubing and spiraling

phy on the right and temporal optic atrophy on the left. Biomicroscopic examination was normal. Tangent screen examination showed a bitemporal defect (Fig. 2). Neuro-, endocrino-, and gynecologic examinations were normal.

No erosion of the sella turcica or any other abnormality was apparent on skull roentgenograms. Carpal ossification was commensurate with the patient's age. Cerebral arteriographic examination revealed a deformed carotid system that suggested pressure inferior and posterior to the bifurcation of the anterior and middle cerebral arteries on the right.

Results of laboratory examinations were: Blood and urine, normal; Kahn test, negative; protein-bound iodine, 6 μg. per cent; inorganic iodine, 1.2 μg. per cent; nonprotein nitrogen, 41 mg. per cent; 17-hydroxysteroids, 3.7 mg. per twenty-four hours; 17-ketosteroids, 9.4 mg. per twenty-four hours; estrogen excretion, 1 rat unit per day; total serum cholesterol, 219 mg. per cent; free cholesterol, 33 mg. per cent; esters, 166 mg. per cent; per cent esters, 75%; and basal metabolic rate, 13%. Lumbar puncture revealed a pressure of 120 mm. of water, a total protein of 18 mg. per cent, and flat colloidal gold and mastic curves; microscopic examination revealed no cells.

In April 1957, a frontal craniotomy was performed after suitable preparation with cortisone. The optic chiasma was approached by following the right greater sphenoid ridge. About 1 cm. anterior to the chiasma, a suprasellar tumor with a bluish hue was found. Needle aspiration of the mass yielded about 10 cc. of dark red blood. As much of the tumor as possible was excised. No complications arose during operation. Administration of cortisone was continued. After operation, the pulse and blood pressure remained high and hyperpyrexia could not be controlled. The patient died eight hours after the operation was completed.

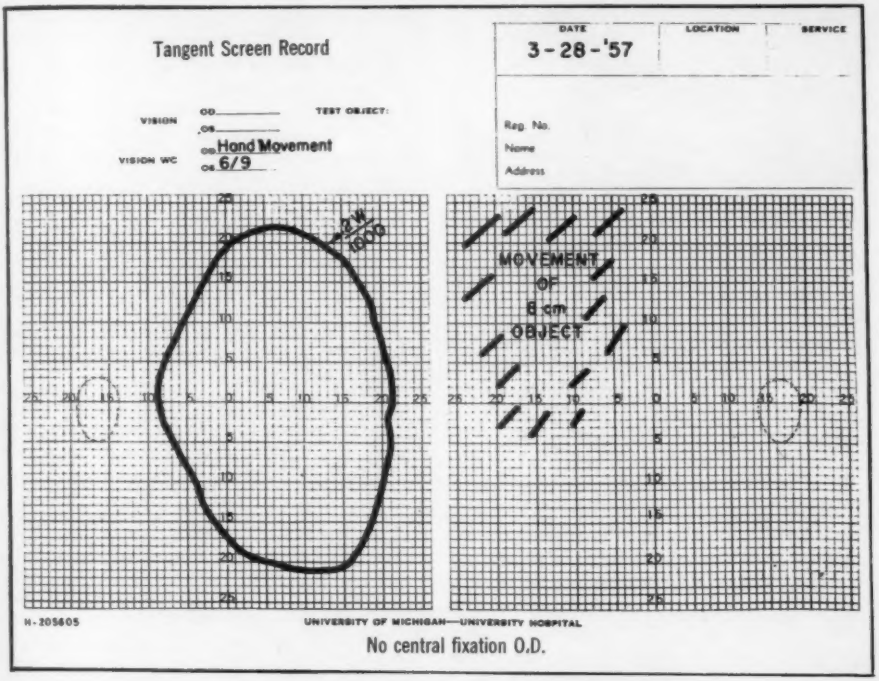

Fig. 2. Tangent screen record showing bitemporal defect

POSTMORTEM FINDINGS

The brain, which weighed 1,520 gm., was swollen, and the convolutions were flattened. The hypothalamic area and infundibulum were prominent and softer than normal. The optic nerves, chiasma, and tracts were firm and definitely enlarged, suggesting that the optic chiasma was invaded by a diffuse glioma. However, this was not confirmed microscopically. The sella was filled partially with a hemorrhagic mass.

HISTOLOGIC EXAMINATION

In the sella turcica, remnants of a chromophobe adenoma of the diffusely growing variety were found besides normal hypophyseal tissue. Examination of the optic nerves, chiasma, and tracts with hematoxylin and eosin and silver carbonate (Scharenberg[5] and Liss[6]) revealed edema of the tissues and marked proliferation of the glial elements. The perivascular glial structures of the optic nerves, chiasma, and tracts were proliferated, and the glial processes surrounding the vessel wall were thickened (Fig. 3).

Reaction of the astroglia ranges from slight proliferation to ameboid degeneration and fragmentation of processes. Appearance of astroglia depends greatly on their location, since morphology of the astroglia differs in various parts of the optic nerves, chiasma, and tracts.[6] The cell body of an astrocyte among normally appearing nerve fibers in the anterior portion of the optic nerve seems to be normal but has thickened processes (Fig. 4). Another astrocyte with an enlarged cell body belongs to the giant variety, which is found in the optic chiasma only (Fig. 5). These cells normally are larger than the others and, when pathologically enlarged, become even more prominent. The pathologic forms of astroglia are accompanied by numerous oligodendroglial cells, many of which are swollen. In the anterior portion of the optic tract, the astrocytes

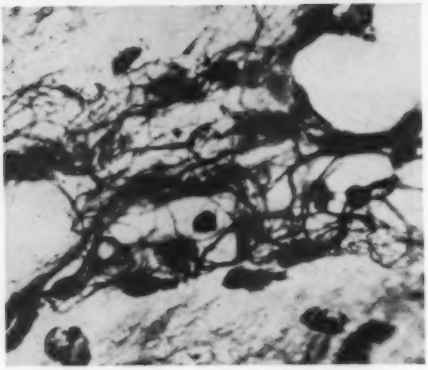

Fig. 3. Photomicrograph showing proliferated perivascular glial structures and thickened glial processes. (× 1,000)

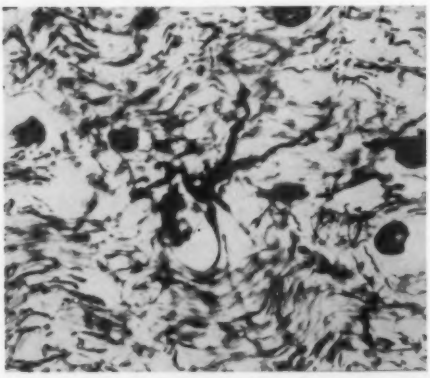

Fig. 4. Photomicrograph showing astrocyte with thickened processes among normally appearing nerve fibers in anterior portion of optic nerve. (× 1,000)

have enlarged bodies and thickened processes. Swollen oligodendroglial elements are scattered among degenerated nerve fibers. Degeneration is extensive along the hypophyseal surface of the midportion of the chiasma.

The presence of swollen oligodendroglia is related to the degree of damage of the nerve fibers. The oligodendrocytes frequently are arranged in a straight line and accompany the damaged nerve fibers (Fig. 6).

Degeneration of astrocytes ranges from slight proliferation (Figs. 4 and 5) to disintegration of the cell bodies and fragmentation of the processes. The astroglial processes follow the direction of the nerve fibers and proliferate along those that are damaged. Frequently, these processes follow the course of the nerve fibers in a tortuous manner or develop numerous small spirals, loops, and knoblike swellings. These swellings do not indicate irreversible astrocytic damage, since numerous thin processes proliferate and maintain supportive function of the astrocyte (Fig. 8). In the final stage of an irreversibly damaged astrocyte, the cell body is shrunken and disintegrating and the processes are thick and fragmented (Fig. 7).

Degeneration of nerve fibers, as previously mentioned, is not generalized, since well-preserved nerve fibers (Fig. 4) as well as destroyed nerve bundles are found in the optic nerve. The medial aspect of the optic nerves shows a typical pattern of degeneration with numerous, beadlike swellings along the course of the fibers. In the final stage of nerve degeneration, the nerve fiber is fragmented, the central fibril is curled, and the surrounding homogeneous material is rounding up (Fig. 9). This type of degeneration will, in time, result in formation of hyaline (cytoid) bodies.

In the described case, proliferation was lim-

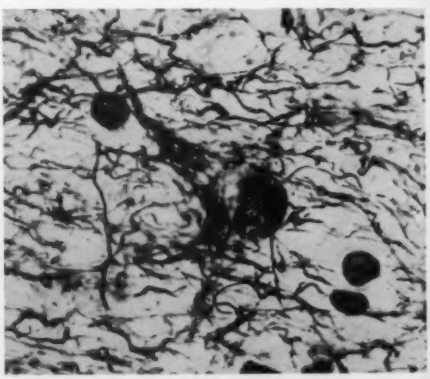

Fig. 5. Photomicrograph showing astrocyte in optic chiasma. The cell body is enlarged, and the processes are proliferated. Several oligodendrocytes are scattered in the field. Note extensive degeneration of nerve fibers. (× 1,000)

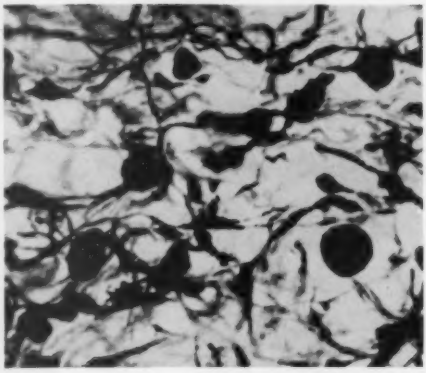

Fig. 6. Photomicrograph showing oligodendrocytes accompanying severely damaged nerve fiber in anterior portion of optic chiasma. (× 1,000)

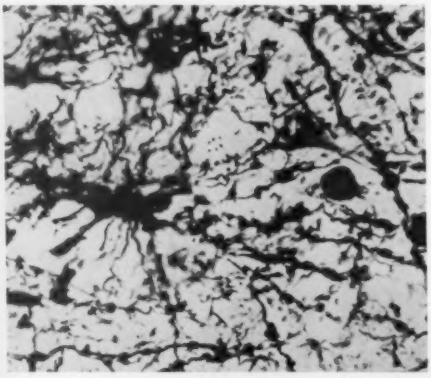

Fig. 7. Photomicrograph showing astrocyte with numerous processes; some are thickened and fragmented, and others are long and fine. (× 1,000)

ited to the glial elements and did not involve the connective tissue.

Pressure from the growing tumor affected the hypothalamus and caused marked proliferation of the astroglial elements and degeneration of the neuronal elements in the hypothalamic nuclei (Fig. 10).

COMMENT

The clinical evaluation of this patient illustrates the difficulties that may be encountered in the early diagnosis of a chiasmal lesion when strabismus and suppression amblyopia, along with a field defect, occur in a young adolescent.

The pathologic findings in this patient are quite different from those in persons with chronic pressure caused by a tumor (Wolter and Liss[7]). Chronic pressure causes atrophy of the compressed nerve, degeneration of the optic nerve fibers, proliferation of astroglia, and oligodendro- and microglial reactions. Similarly, the olfactory bulb and tract respond to chronic pressure caused by meningeal sarcomatosis with gross atrophy and a glial reaction (Liss[8]). The difference between the usual reaction and that noted in the present case seems to be due to the fact that chronic pressure from the chromophobe adenoma induced hypertrophy instead of atrophy of the optic nerves, chiasma, and tracts. The possibility that this change was caused by postoperative edema must be discounted, since, at the time of operation, the optic nerves were unusually thick. The complete lack of a microglial reaction and minimal edema of the oligodendrocytes also suggests that the enlargement was caused by hypertrophy rather than edema. The lack of connective tissue proliferation is unusual, since such proliferation generally is associated with proliferation of glial elements.

The appearance of the perivascular structures that react uniformly throughout the

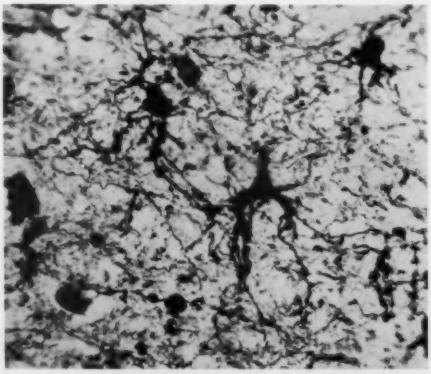

Fig. 8. Photomicrograph showing fragmentation of processes and disintegration of bodies of astroglial cells. (× 1,000)

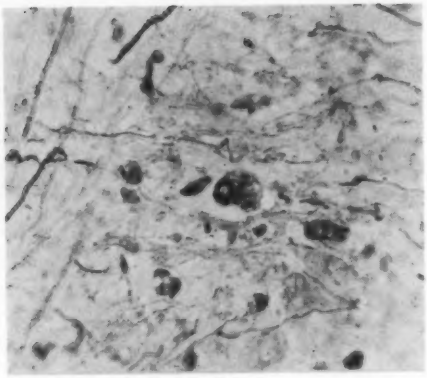

Fig. 9. Photomicrograph showing fragmentation of nerve fiber in posterior portion of optic chiasma. Remnants of neurofibrils can be recognized in the spheric bodies. (× 1,000)

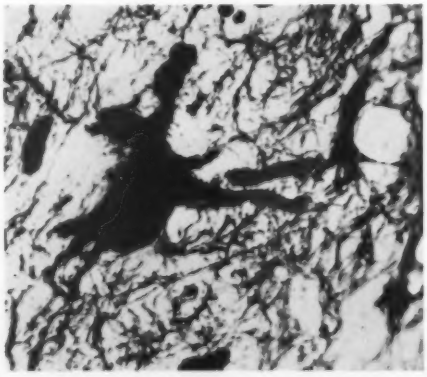

Fig. 10. Photomicrograph showing damaged nerve cell in supraoptic nucleus surrounded by numerous glial fibers. (× 1,000)

nervous system (Wolter[9,10] and Liss[11,12]) indicates that the damage was not extensive, since only slight thickening and decided proliferation of the perivascular glial fibers were noted.

The nerve fiber degeneration follows the typical pattern of degeneration found in the olfactory and optic nerves. The initial stage is characterized by beadlike swellings and is followed by fragmentation and formation of spheric bodies.[13,14]

The pattern of degeneration in the olfactory tract[8] is known to be predetermined by a specific glial cytoarchitecture. Similarly, the different types of astroglia in the optic nerves, chiasma, and tract[6] react differently under pathologic conditions.

SUMMARY

Chromophobe adenoma of the pituitary in a 14-year-old girl produced chronic pressure and gross hypertrophy of the optic nerves, chiasma, and tracts. Histologic examination revealed that advanced degeneration of the nerve fibers was accompanied by decided proliferation and hypertrophy of glial elements.

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Neurology

BOOK REVIEWS

The Clinical Examination of the Nervous System

by G. H. Monrad-Krohn, 11th ed., 466 pp., Ill., Paul B. Hoeber, Inc., New York City, 1958. $9.50

This publication marks the eleventh edition since 1921 of this time-honored guide to the examination of the nervous system. In this revision, the author has had the assistance of the Professor of Medicine in Neurology at the University of Oslo, Dr. Refsum, successor to Monrad-Krohn, now professor emeritus.

In its early editions, it was a small volume, but with the years, it has assumed larger form and expanded content.

While lacking in incorporation of newer knowledge of neurophysiology in areas where the author makes anatomico-physiologic explanations, the book, nevertheless, has much merit as a workable, well-illustrated, descriptive text to aid the student and resident in training in making a neurologic examination.

The author places well-deserved emphasis on the fact that the student should describe what he sees in the examination, rather than merely labeling it.

About half the text is devoted to the description and technics of the examination. The remainder has sections about ancillary examinations. These cover electrical testing, examination of spinal fluid, myelography, examinations for the measurement of intelligence (Binet-Simon)—which has largely been abandoned in this country in favor of the Wechsler-Bellevue—especially for adults), examination for aphasia, vestibular tests, pharmacologic tests, x-ray interpretation, encephalography, ventriculography, electroencephalography, and angiography. A section of anatomic diagrams is included to aid in localization.

If something could be criticized—use of terminology should be improved, modern anatomico-physiologic concepts should be incorporated, and some material should be deemphasized or deleted.

Since this reviewer learned the technic of neurologic examination from the first English edition—a slim volume that fit the white-coat pocket—there is a sentimental bias in recommending this sturdy guide which represents the teaching material of the highly respected, much admired Monrad-Krohn.

M. G. M.

Modern Therapy in Neurology

edited by Francis M. Forster, 792 pp., C. V. Mosby Co., St. Louis, 1957. $12

A book has long been needed which brings to the focus of the medical profession knowledge regarding the therapeutic aspects of neurology as well as the advances being made in such therapy. Dr. Forster, President of the American Academy of Neurology, is to be commended for seeing this need and for making such a book available.

As Dr. H. Houston Merritt states in the Foreword, neurology has been criticized for its interest in diagnosis rather than in therapy, but this criticism could also have been directed toward many of the other medical specialties. Therapy has always been a part of neurology, although it has not received sufficient emphasis. With recent advances in treatment, however, the therapeutic aspects of the specialty must be given additional stress.

The various subjects covered encompass almost the entire field of diseases of the nervous system, and a listing of the authors brings to mind the authorities in the expanding field of neurology in this country at the present time, as well as founders and leaders of the American Academy of Neurology.

Among the topics thoroughly and concisely discussed are the encephalomyelitides, Dr. Knox H. Finley; meningitis, Dr. A. L. Sahs; poliomyelitis, Dr. A. B. Baker; neurosyphilis, Dr. B. J. Alpers; cerebrovascular disease, Dr. Gilbert H. Glaser; multiple sclerosis, Dr. George A. Schumacher; headache, Dr. Arnold P. Friedman; myasthenia gravis, Dr. Lee M. Eaton; diseases of muscles, Drs. Glenn A. Drager and G. Milton Shy; epilepsy, Dr. Forster; diseases of the basal ganglia, Dr. Desmond S. O'Doherty; metabolic and toxic disorders, Drs. R. N. DeJong and Kenneth R. Magee; disorders of cranial and peripheral nerves, Dr. Thomas W. Farmer; degenerative and developmental diseases, Dr. Thomas L. Auth; brain tumors, Drs. R. B. Aird and B. C. Garoutte; trauma, Dr. Benjamin Boshes; rehabilitation, Drs. Pearce Bailey and Marvin Korengold; and the use of tranquilizing drugs in neurology, Dr. Howard D. Fabing.

Clinical aspects of the various diseases are discussed only as necessary to describe treatment. The emphasis throughout the book is on the practical aspects of therapy. All of the authors give the reader the most effective and most advanced aspects of therapy for the individual disease processes. This book is truly a milestone in the progress of neurology as well as in the fight against disease.

A. B. C.

Recent Advances in Cerebral Palsy

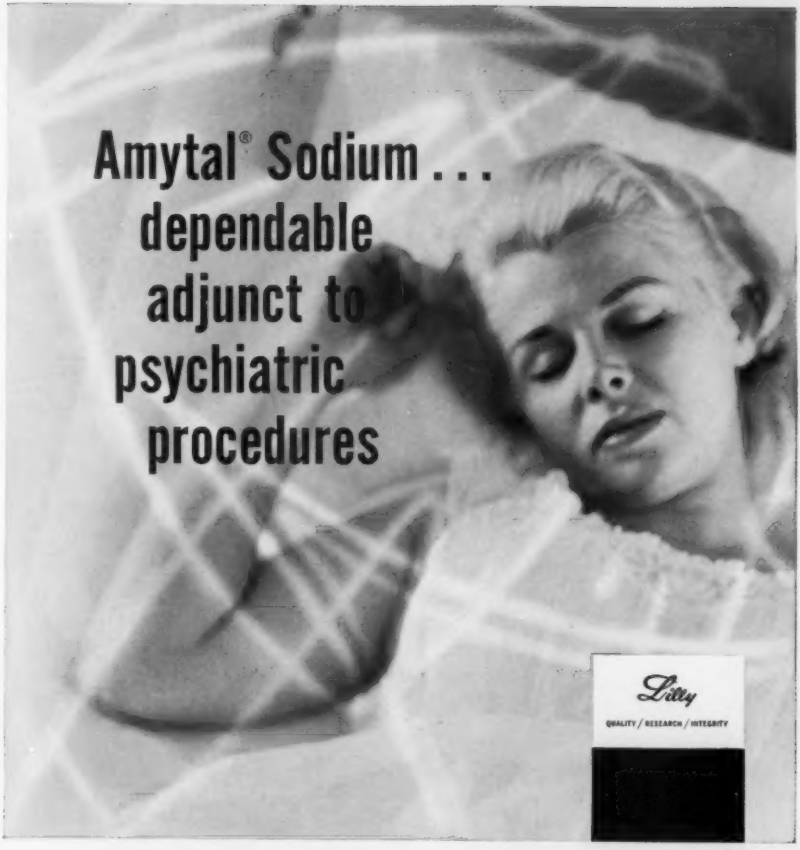
edited by R. S. Illingworth, 389 pp., ill., Little, Brown & Co., Boston, 1958. $2

Present knowledge of cerebral palsy is reviewed by British and American authors. Awareness of the problem has increased, and treatment centers have been developed. However, the greatest postwar advance has been the appreciation for and development of the team approach.

Following a poorly done classification of cerebral palsy are chapters on diagnosis and the psychologic and educational aspects of the disease. A special supplement is included on voluntary and tax-supported services in the United States.

Dr. Russell Meyers, in an interesting chapter, reviews the advances in neurosurgical treatment of cerebral palsy. However, little appears in the book as a whole which can be classified as a recent advance. The summaries are excellent, and the references are well selected.

J.P.R.



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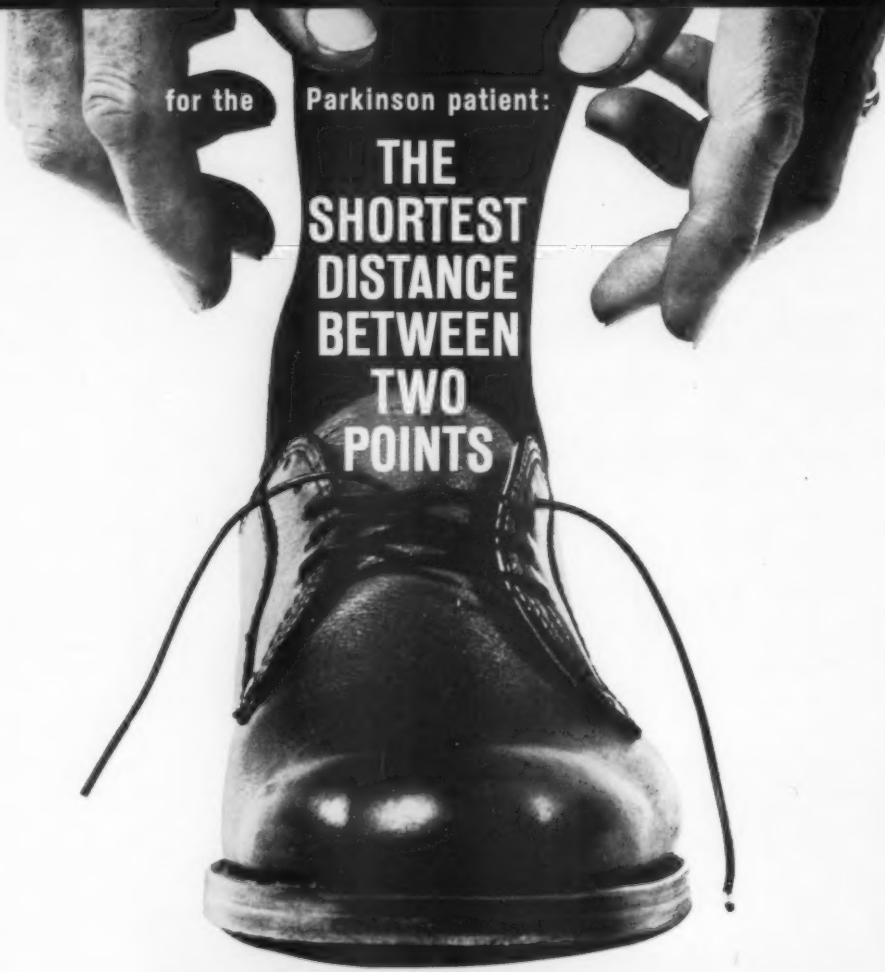

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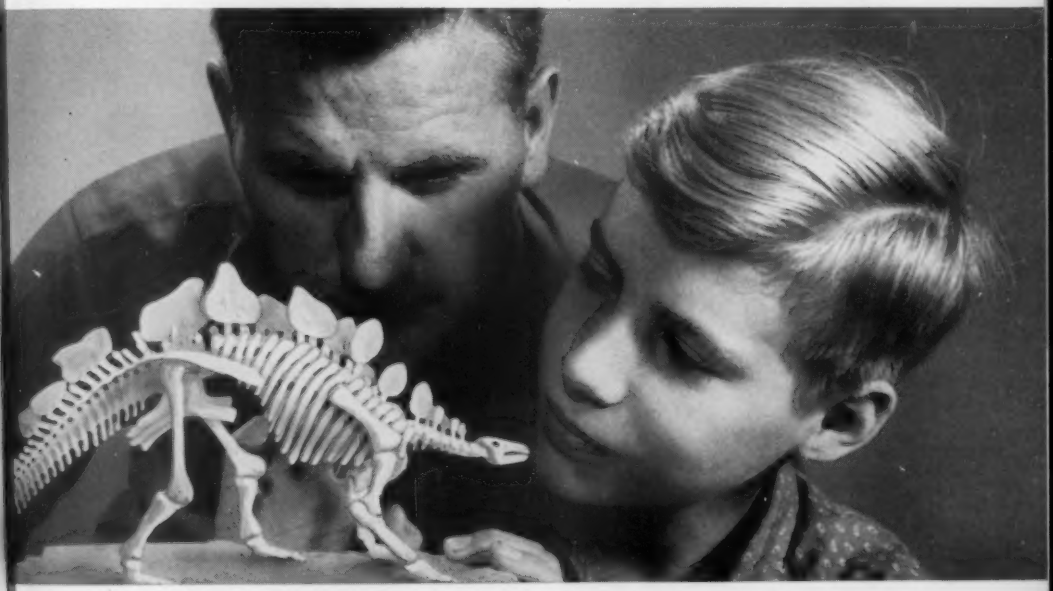

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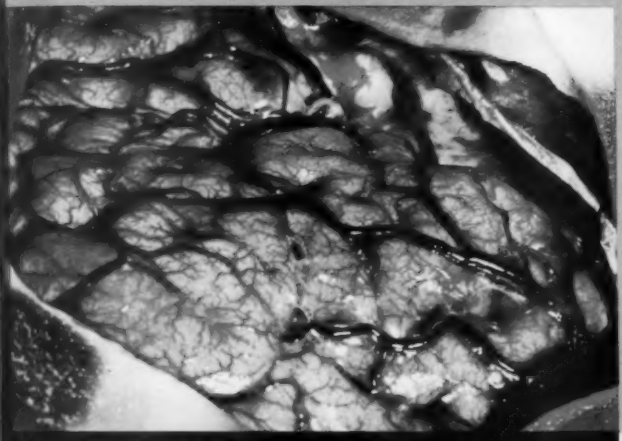

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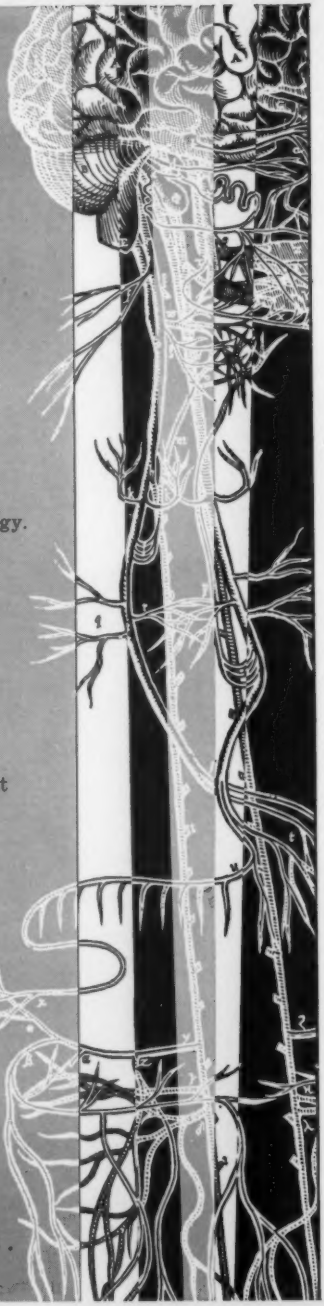

Here is a new approach to the history of neurology. With an historian's eye for the dynamic, the author has chosen to focus on "the great and lasting problems" that have remained inherent in man's endeavor through the ages to understand the functions of the nervous system and their disturbances. By concentrating on fact, thought, and theory, Dr. Riese has achieved a comprehensive picture of neurologic progress.

Dr. Riese traces the history of the doctrine of cerebral localization, its scope, limits, and different versions, both past and present. Other sections of special interest include those on the history of diagnosis, prognosis, and therapy in neurology; and a comprehensive treatment of the history of diaschisis or cerebral shock. Also included are invaluable sections: neurological chronology; list of journals specializing in neurology and neurological societies and associations.

This volume is one of a series devoted to the histories of various specialties and facets of medicine. Félix Martí-Ibáñez, M.D., who wrote the foreword to *A History of Neurology*, is the Editorial Director of the series, which includes Public Health and Ophthalmology.

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JULY 1959

Delegates Convene in Rome for Planning Meetings Rome was the center for the meetings of major planning groups in international neurology early in June. First to convene was the Executive Committee of the WORLD FEDERATION OF NEUROLOGY at the Istituto Superiore di Sanità, Viale Regina Margherita 299 (June 7). Under the presidency of Ludo van Bogaert, 29 delegates of the 35 nations that constitute the WFN met to discuss progress made to date in their current programs and to blueprint future plans....On Monday and Tuesday, June 8 and 9, the delegates to the Seventh International Neurological Congress to be held in Rome in the Fall of 1960 met also at the Istituto Superiore di Sanità under their president, Prof. Mario Gozzano. A summary report of these meetings and the preliminary reunion of the Fourth International Congress of Neuropathology (Frankfurt am Main, June 4 and 5) will be forthcoming in the August issue of the Newsletter.

WFN Newsletter Now in Print The first Newsletter of the World Federation of Neurology was released at the Rome meeting June 7, 1959. It sketches early landmarks in the Federation's history; summarizes the progress made in the attainment of its objectives for the advancement of neurology, as a center for the exchange of news and scientific knowledge, and in its plans for the publication of WORLD NEUROLOGY; and also delineates the present role of the WFN in the organization of international symposia and congresses, its progress in the stimulation of international neurologic research, and its plans for the promulgation of conferences and collaborative research projects in the growing field of geographic neurology. It also contains items of neurologic news around the world, a series of personal briefs, and a schedule of coming neurologic meetings....Copies of the first WFN Newsletter may be obtained by AAN members by writing to Dr. Pearce Bailey, Secretary-Treasurer General, World Federation of Neurology, National Institutes of Health, Bethesda 14, Maryland.

Bill for International Medical Research Passed by the Senate The Senate passed a bill introduced by Lister Hill (D., Ala.) as a Senate joint resolution (S.J. Res. 41) for the creation of a National Institute for International Medical Research by a vote of 63 to 17. This measure is now pending action

in the House. The new legislation would establish the Institute within the framework of the National Institutes of Health of the Public Health Service....Informed political sources believe that the bill will be passed during this session of the Congress, but probably no appropriation will be made available until the next session.

Conference on Auditory-Vestibular Mechanisms Held in Bethesda

A three-day conference on neural mechanisms of the auditory and vestibular systems was held in Bethesda June 11-13, under the auspices of the National Institute of Neurological Diseases and Blindness. William F. Windle (NINDB) chaired the scientific program attended by 27 scientists from both here and abroad. The Conference was opened formally by Richard L. Masland (NINDB) at the subscription dinner followed by an after-dinner paper by Georg von Békésy (Cambridge, Mass.) on "Experiments on the Mechanism and Function of the Cochlea." The scientific sessions on auditory mechanisms, which began the next day (June 12), were opened by Hallowell Davis (St. Louis) with a paper on "Mechanism of Excitation of Auditory Nerve Impulses," which was followed by presentations from Ichiji Tasaki (NINDB); Hans Engström (Göthenborg, Sweden); A. de Lorenzo (Baltimore); H. F. Schuknecht (Detroit); and Stacy R. Guild (Baltimore). Among those participating in the afternoon sessions (June 12), were G. L. Rasmussen (NINDB); Jerzy E. Rose (Baltimore); Robert Galambos (Washington, D. C.); Clinton Woolsey (Madison); A. R. Tunturi (Portland); J. E. Hind, Jr. (Madison); and W. D. Neff (Chicago)....The final day of the Conference was devoted to vestibular mechanisms. These sessions were opened by Alf Brodal (Oslo) with a presentation on the "Fiber Connections of the Vestibular Nuclei." He was followed by contributions from Jan Wersäll (Stockholm); G. F. Dohlman[1] (London); R. R. Gacek (NINDB); J. Lindsay (Chicago); César Fernández (Chicago); M. B. Carpenter (New York); and Bo E. Gernandt (NINDB)....A round table discussion of gap areas, opened by R. B. Livingston (NINDB), concluded the conference.

Brain Bank Established for Parkinson's Disease Research

At a special luncheon meeting held in the Louis XVI Room of New York's St. Regis Hotel, Mr. William Black, President of the Parkinson's Disease Foundation, announced the establishment of a "Brain Bank" in the Foundation's headquarters. The "bank" is to provide brains of deceased Parkinson's disease sufferers to neurologists and other scientists engaged in Parkinson's Disease Foundation scientific research investigations. The project will also provide opportunity for detailed studies of pathologic changes at various stages of Parkinson's disease. The Foundation is asking Parkinson's patients who wish to donate

[1]Currently a Visiting Scientist at NINDB.

their brains posthumously to science to communicate with the Foundation's headquarters at 125 East 50th St., New York 22, N.Y. Thereafter, the Foundation will undertake all details and expenses involved in making this material available to selected scientists working in this field....Among the neurologists interested in this project are: H. Houston Merritt, Robert S. Schwab, William K. Jordan, Russell Meyers, Francis M. Forster, Augustus S. Rose, and S. Bernard Wortis. The Foundation's Medical Director is Melvin D. Yahr.

Brady Appointed Medical Director of Muscular Dystrophy Group Dr. J. Morrison Brady has been appointed Medical Director of the Muscular Dystrophy Associations of America. He will head the Association's medical and scientific activities, with responsibility for processing its grants program in research and for supervising both its network of clinics and the other patient services that the MDAA provides through its more than 360 chapter affiliates. Previously, Dr. Brady was affiliated with the National Foundation for Infantile Paralysis, where he was Acting Director of Medical Services and Chief of the Field Medical Service Division. He has had a broad medical experience in both hospital administration and medical research....The MDAA conducted the dedication ceremonies of its new Institute for Muscle Disease in New York City, June 13, in which 500 representatives of the MDAA's chapters throughout the country participated. The new Institute, located in the community of the New York Hospital -- Cornell Medical Center will be devoted to basic and clinical research in problems of MD. Its staff will consist of some 50 top investigators and approximately 100 laboratory technicians.

Committee on Neurologic Disorders in Industry Met in Atlantic City The Committee on Neurologic Disorders in Industry of the Council on Industrial Health of the American Medical Association met in the Claridge Hotel, Atlantic City (June 12). The program included reports and discussions of such problems as a functional capacity classification (based on ability rather than disability) of neurologic disorders; industrial employment problems in this field; over-all statistics of neurologic diseases in the U.S.A.; licensing of automobile drivers in Wisconsin; compensation information; and insurance company attitudes. This meeting of the Committee was a sequel to its organizational meeting held in Cincinnati (February 13) where the problems as reported at Atlantic City had originally formulated and where workshops were organized with industrial physicians. The principal objectives of this Committee are to improve conditions and mutual understanding between employers and employees suffering from neurologic disorders....The members of the Committee are: Melvin D. Yahr, Chairman; Pearce Bailey; Benjamin Boshes; Francis M. Forster; Augustus S. Rose; Harry Sands; Theodore Schwade;

Robert Garber, and Harry E. Tebrock. Representing the AMA Council staff are B. Dickson Holland and Lee N. Hames.

Barraquer-Ferre Dies in Barcelona On February 21, 1959, at 71, Luis Barraquer-Ferré, noted Spanish neurologist, died after a short illness in Barcelona. An honorary corresponding member of the Academy, Barraquer-Ferré formerly was Physician-in-Chief of the neurologic service at the Holy Cross and St. Paul's Hospital in Barcelona, where many Spanish neurologists were trained. He was the son and disciple of the distinguished neurologist Luis Barraquer-Roviralta. In 1952, a special volume of the "Arquivos de Neuro-Psiquiatria" was printed to honor his 65th birthday. In his later years, Luis Barraquer-Ferré collaborated extensively with his neurologist son and disciple, Luis Barraquer Bordas (Lauria, 102, Barcelona), who was kind enough to furnish the announcement of his father's death.

Briefs The fourteenth annual convention of the Society of Biological Psychiatry was held at the Claridge Hotel, Atlantic City (June 12 to 14) under the presidency of Joseph Wortis....As of September 1, 1959, Orville T. Bailey, Professor of Neuropathology at the Indiana University School of Medicine, will become Professor of Neurology at the University of Illinois College of Medicine in Chicago....The European reunion of Electroencephalography, called the Marseille Colloquium, to be held in Marseille October 5 to 10, under the direction of Henri Gastaut....Among the distinguished neurologic scientist visitors to the United States recently were: A. Subirana (Barcelona); Róman Arana-Iñiguez (Montevideo); Wladyslaw Jakimowicz, Professor of Neurology of the University of Krakow, Poland, who has been visiting this country under the auspices of the Rockefeller Foundation.

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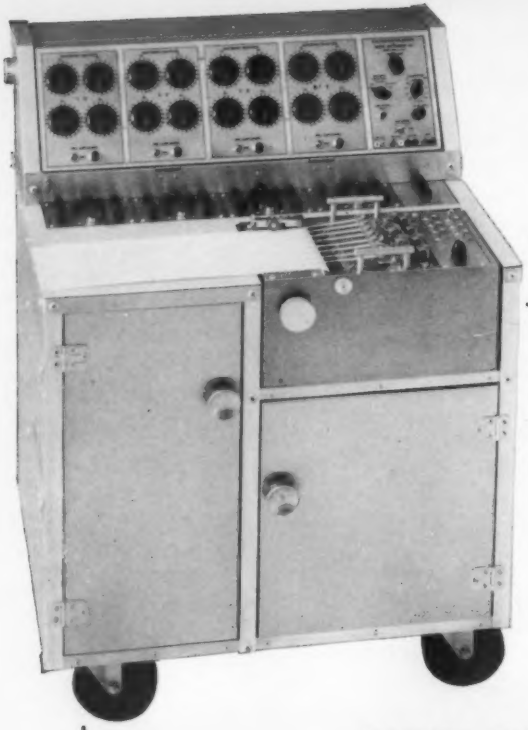

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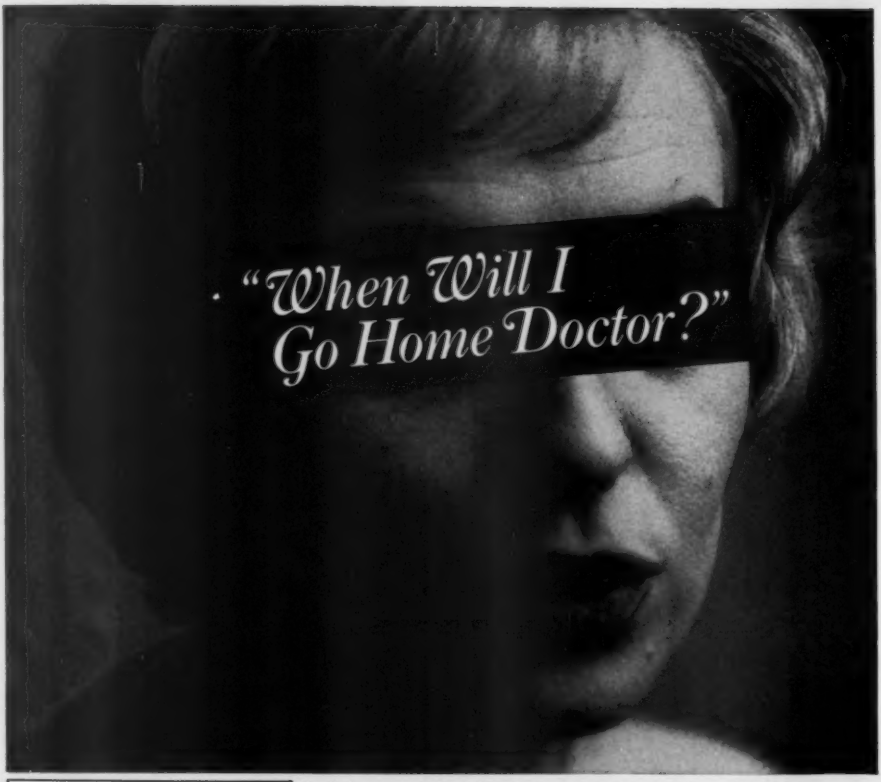

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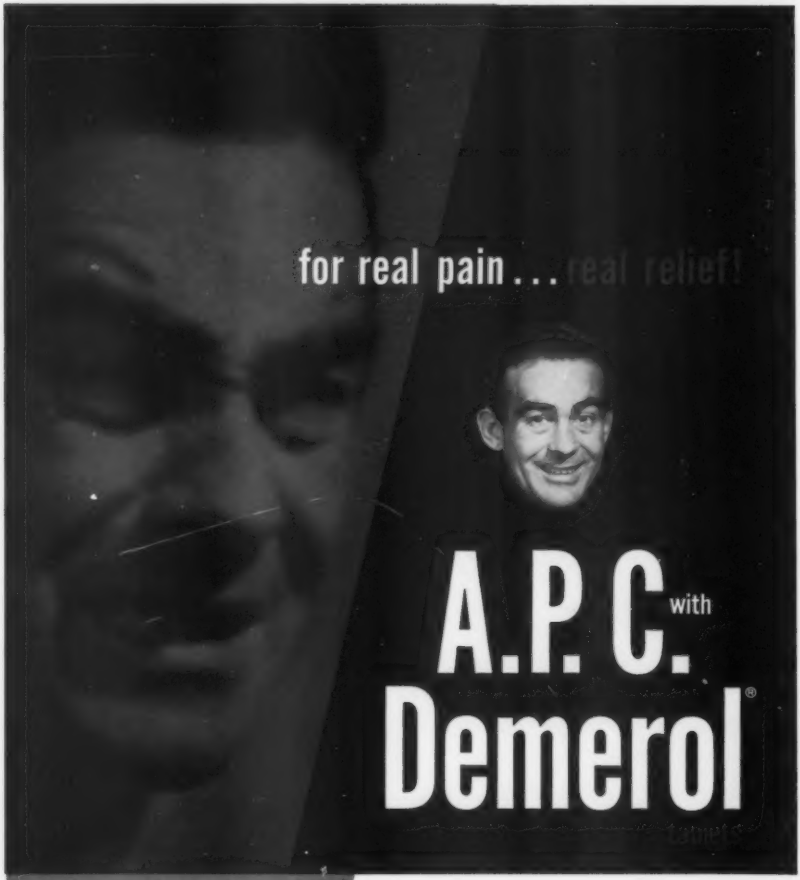

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